

THE MEDICAL CLINICS OF NORTH AMERICA

NOVEMBER 1973

ACUTE MEDICINE

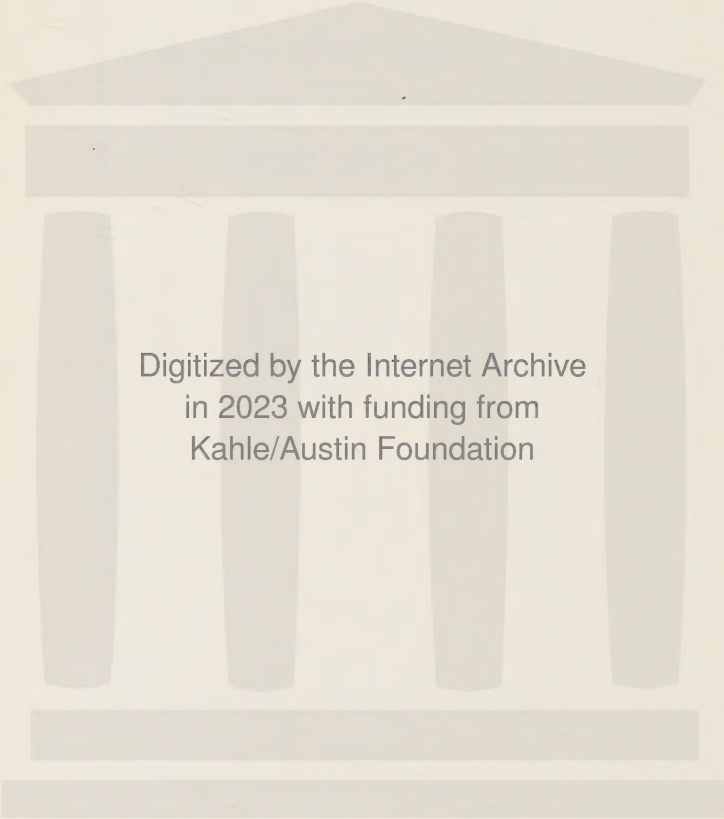
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THE MEDICAL CLINICS OF NORTH AMERICA

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SYMPOSIUM ON
ACUTE MEDICINE

Lawrence Sherman, M.D., and
Howard D. Kolodny, M.D., *Guest Editors*

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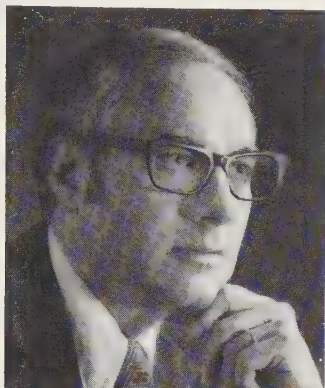
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La Moutte-Teunissen

LAWRENCE SHERMAN, M.D.



HOWARD D. KOLODNY, M.D.

Foreword

The municipal hospitals of New York City originate from a six-bed infirmary built in lower Manhattan in 1736. This infirmary, an appendage to a workhouse, was the first public hospital in the American colonies. In 1811 it was replaced by a new building at a site called "Bellevue." In 1929 that hospital and some others were consolidated into a unified group. Today, 19 hospitals form the municipal hospital system of New York, the largest nonfederal hospital system in the United States. Its immensity can best be captured here by a recital of some vital statistics: 15,000 hospital beds, 7,500 staff physicians, an annual budget now of nearly a billion dollars (exceeding the combined *total* expenditures of Atlanta, Cleveland, Minneapolis, and Seattle), and a committed capital budget program of over a billion dollars. Other awesome statistics tell why it is appropriate for this issue on acute medicine to originate from these municipal hospitals: in 1972 they treated 2 million people who made 1.67 million emergency room visits and 9 million hospital visits of all types.

In the last decade, diagnosis and treatment of even the most time-worn acute medical problems have been transformed by technological advances and new insights into pathophysiology. This transformation is reflected in these pages. Articles on such important topics as acute chest pain, life-threatening cardiac arrhythmias, and acute respiratory failure are accompanied by corollary articles on newer diagnostic and therapeutic methods. The topics include noninvasive techniques in diagnosis and treatment of acute cardiac problems, and types and uses of cardiac

pacemakers and mechanical respirators. This transformation of treatment is apparent in many other articles—perhaps most dramatically in those on urban tetanus and acute renal failure.

The reader will also find a bonus in the form of answers to some tantalizing questions. Among these are the meaning of the “doll’s eye” reflex in unconscious patients (p. 1369); the cardiac arrhythmia that is now the leading cause of death in tetanus, and how to treat it (p. 1378); the five skin lesions characteristically found in bacterial endocarditis (p. 1386); the mechanisms producing hyponatremia in congestive heart failure (p. 1426); why some patients with insulinoma have diabetic glucose tolerance (p. 1451); how changes in left ventricular ejection time may predict survival or death after acute myocardial infarction (p. 1493); and the blood gas determination that may signal bronchial mucous occlusion in acute asthma, demanding immediate additional treatment (p. 1545).

It is the purpose of this symposium on acute medicine to help the doctor on the spot to proceed knowledgeably and with all deliberate speed. We thank the contributors—physicians working at nearly every municipal hospital in all corners of New York—for sharing their knowledge and experience. Because of their labors, we know the reader will find the symposium a welcome reference when he or she becomes that doctor on the spot.

In our own labors for this issue we received unstinting secretarial assistance from Joy Wendling. We gratefully acknowledge her help.

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Evaluation of the Unconscious Patient

*L. P. Hinterbuchner, M.D.**

PHYSIOLOGY OF CONSCIOUSNESS

In order to understand better what conditions alter the state of consciousness, it is necessary to review briefly the pertinent neurophysiology. For greater detail, the reader is referred to the review by Plum and Posner.³

Consciousness has two components, content and the "on-off" system. Content is provided by the higher cerebral functions and includes memory, thought, orientation, and emotion, as well as the facilities for communication with the external world through language, auditory and visual comprehension, skilled movements, and complex responses. All these functions depend on the integrity of the hemispheres. Selective localized dysfunction of any part of the cerebral cortex or hemisphere may produce a neurologic deficit in the appropriate function without necessarily impairing the state of consciousness. However, the larger the area of dysfunction, the greater is the resulting constriction of the content of consciousness.

The crude "on-off" quality of consciousness may be likened to a switch which activates the cerebral cortex so that it can produce the content of consciousness. The switch is apparently provided by the ascending reticular activating system, a multisynaptic mass of neurons located primarily in the brain stem extending from the pons through the midbrain to the thalamus. Interruption of activity in this system results in a state of unconsciousness. The primary lesion need not be in this area as long as the remote effects of the lesion render this area ineffective. Thus, a supratentorial expanding space-occupying lesion may produce a tentorial herniation, compress the midbrain, and result in clouding of consciousness. On the other hand, a metabolic or toxic abnormality such as barbiturate poisoning or hypoglycemia may produce unconsciousness by affecting both the hemispheres and the ascending reticular activating system.

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Commonly, the brain stem is affected by cerebral herniation. Three types of supratentorial herniations are recognized: cingulate, central transtentorial, and uncal. In cingulate herniation the midline structures are displaced under the falx to the opposite side. This alone does not affect the state of consciousness and, therefore, requires no comment. In central transtentorial herniation the entire diencephalon is displaced downward into the tentorial notch, producing diencephalic and then midbrain dysfunction. In the uncal herniation the uncus hippocampi is displaced medially and downward, causing a lateral compression of the midbrain.

Of the uncal and central herniations the uncal has more characteristic signs. The initial stages are marked by unilateral features, a dilated pupil, always ipsilateral to the compressed side, and pyramidal signs usually contralateral. At times, especially with subdural hematoma, the pyramidal deficit may be ipsilateral to the side of the lesion. The rate of progression may be rapid leading quickly to failure of the midbrain and deepening coma.

Central herniation is more insidious and amorphous. In the initial (diencephalic) stage, one may see merely confusion, disorientation, and drowsiness. Headache may be prominent and incontinence is common. Cheyne-Stokes respiration, small reactive pupils and hyperthermia may be present. Later, as the midbrain becomes involved, the drowsiness deepens, the pupils become mid-dilated and poorly reactive, and the reflex upward movements of eyes may be impaired, with otherwise intact oculoccephalic movements. Bilateral and at times asymmetric pyramidal tract signs may appear. Eye movements may be normal, or dysconjugate. With further progression either type of herniation leads to further failure of midbrain, then the pons and ultimately the medulla.

Infratentorial mass lesions also may displace cerebral tissue, resulting in either a direct compression of the brain stem or an upward tentorial herniation, or a downward herniation into the foramen magnum—a life-threatening situation.

The consequences of the displacement are threefold: First, there is dysfunction of the displaced tissue by compression or traction. Second, the vessels in the area of the compression are compromised, causing ischemia in the appropriate vascular territory. Third, if the herniation persists, secondary hemorrhages will occur below the level of herniation, converting a potentially reversible condition into an irreversible one. It is this last complication which makes the transtentorial herniation so treacherous, especially in cases of otherwise treatable lesions such as subdural hematoma.

EVALUATION OF THE UNCONSCIOUS PATIENT

A complete evaluation includes data from history, general physical and neurologic examination, laboratory studies, and special procedures when indicated.

Some history can usually be obtained from witnesses or relatives.

The initial observations by the ambulance driver and the emergency room personnel may also be of considerable value.

The physical examination differs from that of a conscious patient for obvious reasons. The patient should be examined for signs of trauma, systemic organ disease, metabolic disease, and intoxications. In observing the general condition one is concerned with temperature, cardiovascular status, urinary output, odor of the breath, needle marks on the extremities. Decubiti will suggest prolonged recumbency resulting from inability to move because of unconsciousness or paralysis.

External signs of injury may indicate either trauma to the head or seizures. Palpation may reveal depressed skull fracture. Blood or cerebrospinal fluid in cranial orifices may indicate fracture of the base of the skull. Fractures elsewhere in the body may not be readily recognized in a comatose patient unless specifically looked for.

Laboratory studies should routinely include blood sugar, blood urea nitrogen, barbiturate determination in serum and urine, electrolytes, and hemogram. Not routine but frequently utilized studies are blood gases, pH, and osmolality determinations, as well as liver, kidney, lung, and cardiac investigations. Search should be made for infections, sepsis, intoxications, deficiency states, and malignancy. More rarely, endocrinologic studies have to be carried out.

Of the special neurologic studies, the lumbar puncture is almost routine, the only fear being that of aggravating an existing cerebral tissue herniation. Lumbar puncture is indispensable in detecting central nervous system infections or hemorrhagic processes. The spinal fluid examination should always include determination of cells and protein; sugar is helpful especially in infections or malignant diseases.

The electroencephalogram is of great help in deciding whether the process is diffuse or focal, destructive or irritative. It is also used to determine brain death. The static and dynamic brain scan is an excellent screening tool in cases of subdural hematoma and of vascular malformations. It is also helpful in various vascular, inflammatory and neoplastic diseases. The echogram is not utilized frequently, even though the method has been available for many years. It is of value in experienced hands only.

The decision regarding angiograms and air studies is best left to the clinical judgment of the neurologist or neurosurgeon. The benefit of these procedures must be weighed against their risks.

NEUROLOGIC EVALUATION

Neurologic evaluation includes grading of the consciousness, evaluation of respiration, meningeal signs, and clues of localizing value (position of head and eyes, vision and fundi, pupillary spaces, eye movements, motor and sensory responses). Serial examinations are necessary to determine progression or deterioration and the need for further action.

Grading Impaired Consciousness

Meaningful communication about the depressed state of consciousness requires clarification of the terms commonly used. Expressions

such as semiconscious, semicomatose, or semistuporous are meaningless unless better defined.

A useful classification includes four basic terms: the state of alert wakefulness, drowsiness, stupor, and coma. These should be used only as a rough guide as it is preferable to describe the state of consciousness in terms of the patient's spontaneous behavior and responses to external stimuli.

The patient who is fully conscious is in a state of alert wakefulness. Such a patient clearly appreciates his environment and responds quickly and appropriately to visual, auditory, and somatosensory stimuli.

The drowsy patient appreciates his environment less, his responses are appropriate but delayed and slow. He is rousable by minor stimuli, often verbal but he may neglect some of them altogether. The patient is capable of responding verbally unless aphasic, aphonic, or anarthric. Lethargy and obtundation are synonyms used by some to denote a greater degree of drowsiness.

The stuporous patient is rousable by intense stimulation only. Loud shouts may elicit a minor nonverbal reaction. The motor response is usually well formed and recognizable as defensive or complex purposive movement, unless the patient is paralyzed. Reflex reactions are usually preserved.

The comatose patient does not perceive his environment and even intense stimulation produces poor, primitive, or rudimentary motor responses (moderately deep coma), or no responses at all (deep coma). Reflex reactions are entirely dependent on the location of the lesion.

Respiration

Often the unconscious patient is already on a respirator when first seen. It is then necessary to disconnect the respirator briefly in order to determine whether spontaneous breathing is present. Its absence is of grave prognostic significance.

Spontaneous respiration may be affected by a multitude of conditions. However, some types of respiratory abnormalities may signify central nervous system dysfunction (Table 1):

Table 1. *Localizing Value of Respiratory Patterns in the Unconscious Patient*

LOCATION	RESPIRATION
Bilateral cerebral (upper brain stem)	Cheyne-Stokes
Low midbrain Upper pons	Central hyperventilation
Pons	Apneustic Irregular (ataxic)
Medulla	Gasping Depressed (shallow)

Cheyne-Stokes respiration. The well known alternation between hyperpnea and apnea with crescendo and decrescendo transition between the two is seen with bilateral lesions of the internal capsule or basal ganglia. Rarely the dysfunction may be in the upper brain stem. The increase in the responsiveness to carbon dioxide is responsible for hyperpnea and the impaired ventilatory stimuli coming from the forebrain are responsible for the apnea. Cheyne-Stokes respiration is most commonly seen in metabolic diseases, in bilateral cerebral vascular occlusive disease, and in toxic states, among others. During the apneic state, responses to pain, to visual threat, or the corneal reflexes may decrease or vanish altogether only to reappear during the hyperventilatory phase. The impaired state of consciousness becomes even further depressed during the apnea.

Central neurogenic hyperventilation is a sustained deep rapid hyperpnea and is seen with tegmental dysfunction of the lower midbrain or pons. Lesions in this area, hypoglycemia, anoxia, or compression due to a supratentorial mass is usually responsible for this relatively infrequent respiratory pattern.

Apneustic breathing consists of periodic prolonged inspiratory phase followed by apnea and is suggestive of a lesion in the pons.

Irregular (ataxic) breathing consists of irregular and unpredictable breathing movements. It is probably the result of interruption in the reciprocal relationship between the inspiratory and expiratory centers as well as depressed responsiveness of these centers. Sleep or mild sedation may induce periods of apnea in these patients. The dysfunction is in the lateral medulla.

Gasping respiration may be slow, irregular, deep, or sometimes consist of several quick inspiratory phases followed by apnea. It is seen in medullary lesions.

Depressed respiration consists of shallow respiratory movements of inadequate amplitude and is seen in medullary depression usually toxic in nature.

Meningeal Signs

Stiff neck, pain produced by passive manipulation of the head, Kernig or Brudzinski signs may indicate that the unconscious is associated with meningeal irritation due to bleeding or infection. Absence of meningeal signs in a profoundly comatose patient does not rule out meningeal irritation.

Position of the Head and Eyes

In paralytic lesions of the hemispheres, particularly those involving the frontal lobe or the outflow therefrom, the head and eyes often turn to the side of the lesion and away from the hemiplegia. At times a homonymous hemianopic field defect may contribute to the deviation of head and eyes if the patient is not completely unconscious. In such case, the visual stimuli from the unaffected field of vision attract the patient's attention. In lesions of the brain stem, after the corticofugal fibers have crossed, the patient's head and eyes may be turned toward the side of the hemiplegia.

Vision and Fundi

If the drowsy patient responds to visual threat by blinking, but the response is asymmetric, this may indicate a homonymous field defect. When the response is absent, one cannot be certain whether this is due to decreased vision or depressed state of consciousness. Fundusoscopic examination will detect papilledema or retinal hemorrhages. Subhyaloid hemorrhages are sharply outlined, localized and shiny. They usually signify a rapidly developing hemorrhagic catastrophe within the head.

Pupillary Spaces

Pupillary size, accommodation, and reaction to light and to pain provide further localizing clues. Pupillary dilatation results from involvement of the oculomotor nerve or of the Edinger-Westphal nucleus, representing the parasympathetic outflow. Incomplete functional disruption may produce an entire spectrum of changes from mildly asymmetric pupils to the widely dilated but still slightly reactive pupil. A dilated pupil in a comatose patient suggests the following principal locations of the lesion: (1) at the junction of the carotid and the posterior communicating artery where an aneurysm may compress the third nerve as it passes towards the orbit; (2) at the midbrain where the third nerve may be involved by a variety of lesions within the midbrain or by compression from without, for instance uncal herniation.

A lesion in the midbrain affecting the sympathetic and parasympathetic outflows produces a mid-dilated pupil, not reactive to any stimuli. When the sympathetic outflow is affected, the pupil becomes constricted (Horner's syndrome). A pontine lesion, usually a hemorrhage, produces very small pupils, the result perhaps of a combination of parasympathetic irritation and sympathetic paresis. A lesion affecting the lateral sulcus of medulla oblongata may also produce pupillary constriction.

The reaction of accommodation is part of the near reflex,¹ consisting of convergence, accommodation of the eyes, and miosis. It is tested by inducing convergence of the eyes, and the response is miosis. In an unconscious patient pupillary responses to eye movements may be observed as long as the eyes are not immobile, but if the patient's eyes move continuously it may be difficult to determine whether the change in the pupillary size is due to eye movements or other stimuli. The reaction of accommodation is impaired with midbrain lesions.

The reaction to light is most commonly impaired by pretectal lesions, but retinal hemorrhages and optic nerve involvement may also decrease the response to light.

The reaction to pain, the so-called ciliospinal reflex, consists of a pupillary dilatation in response to noxious cutaneous stimulation of the neck. This is mediated through the sympathetic outflow. When preserved it presumably indicates that the lower brain stem is intact, provided that the sympathetic pathways in the cervical and upper thoracic cord and the cervical sympathetic chain are functioning.

Variable response of pupils to light suggests toxic or metabolic abnormality rather than structural lesion of the brain stem. Fixed dilated

pupils are usually due to irreversible structural lesions. Certain drugs produce definite pupillary changes: atropine and similar drugs paralyze the pupil in dilatation, opiates produce very small, barely reactive pupils, glutethimide may produce midposition pupils, often fixed to light.

Eye Movements

The position of the eyes at rest has already been discussed. Ocular motility can and should be examined. A stuporous patient may have a slight divergent strabismus. If the patient is rousable even slightly, the strabismus may correct itself, suggesting that there is no structural lesion. A variety of eye muscle and lid palsies associated with structural lesions of the brain stem are outside of the scope of this article. However, two reflexes and spontaneous eye movements will be discussed.

Oculocephalic reflex, or "doll's eye" phenomenon, is the movement of the eyes in response to head movement. It is produced by passive turning of the head from side to side or up and down. It is preserved if there is no structural or functional impairment of the vestibular or proprioceptive connections to the oculomotor system. In such cases when the head is moved horizontally the eyes will oppose the direction of the head movement and will turn in the eye socket toward the opposite side. Likewise, upon extension of the head the eyes deviate downward and upon flexion of the neck the eyes deviate upward. In severe depression of the brain stem function, the eyes remain fixed relative to the orbits.

Oculovestibular reflex is the eye movement in response to caloric stimulation. When present, even in the unconscious patient, it suggests preservation of functional integrity of pons and midbrain containing the vestibulo-ocular connections. With the head at 30° above the horizontal (and provided the tympanic membrane is intact) instillation of cold (30° C) or iced water will normally produce a slow deviation of the eyes to the same side and quick nystagmus to the opposite one. Warm water (44° C) produces the opposite effect. When both ear canals are irrigated with cold water simultaneously the eyes will deviate downward, with quick nystagmus upward. Warm water will produce the opposite effect. The best mnemonic device designed to remember the normal horizontal movements is represented by the word COWS, standing for "cold opposite, warm same". It is important to remember that this refers to the quick component of the nystagmus. In an unconscious patient with intact brain stem functions, the quick component is abolished. The caloric stimulation then produces appropriate slow eye movements (Table 2).

Spontaneous eye movements. Rolling eyes consist of slow conjugate

Table 2. Oculovestibular (Caloric) Responses

EAR IRRIGATION	SLOW EYE MOVEMENTS	QUICK EYE MOVEMENTS
Cold Unilaterally	Ipsilateral	Contralateral
Warm Unilaterally	Contralateral	Ipsilateral
Cold Bilaterally	Both Down	Both Up
Warm Bilaterally	Both Up	Both Down

or disconjugate movements suggesting absence of structural lesions. In deeper coma these disappear. A variety of nystagmoid movements can also be seen but are relatively rare in unconscious patients.

Motor System

Observed movements may occur either spontaneously or in response to stimulation.

Spontaneous movements may be seen in all patients except those in deep coma. Major generalized and focal seizures are easily recognized but minor seizures may go undetected. They may consist of occasional deviation of the eyes or abrupt minor movements of face, eyes, lids, or peculiar facial expressions. Such movements are to be considered seizures if they are paroxysmal with a distinct sudden onset and sudden end. Diffuse myoclonic twitches are often seen with metabolic or widely scattered anoxic lesions such as in postanesthetic complications. Still other seizures may take the form of slow movements such as deviation of head and eyes, but unless they proceed to the clonic phase, they can be misinterpreted as either voluntary or involuntary movements. Other spontaneous movements may be recognized as volitional. When limited to one side of the body they suggest paralysis of the opposite limbs.

Motor responses to stimulation may be classified in three groups: (a) Formed complex movements, often recognizable as purposeful or defensive; (b) Incomplete or rudimentary. At times it may be difficult to determine whether these movements are defensive, degraded merely by the degree of stupor rather than secondary to a lesion affecting the motor system. Rudimentary movements on one side only, while those on the other are well formed, suggest paresis. Other rudimentary movements may be of reflex nature. (c) Reflex movements, either spontaneous, occurring without any apparent stimulus or produced by stimulation. Actually all reflex movements require a stimulus, however this may be endogenous or produced by ambient noises, vibrations, etc.

The following types of reflex movement are of importance:

Decorticate movements and postures consist of flexion and adduction in the upper extremity (including the wrist and fingers), and extension of the lower extremity with internal rotation. These postures are reminiscent of chronic spastic hemiplegia and are believed to be the result of a lesion of the pyramidal tract just rostral to the midbrain, disconnecting the hemispheres from the upper brain stem. When present, such movements suggest a large lesion usually involving the internal capsule or the rostral cerebral peduncle on the opposite side. Often the thalamus and its adjacent structures may be involved.

Decerebrate movements and postures consist of adduction, extension, and pronation of all four extremities. When fully developed, the decerebrate state includes opisthotonus. It is best thought of as an exaggerated posture of standing. Decerebration is most commonly seen with lesions destroying or compressing the midbrain or with lesions affecting the upper pons. The dysfunction is between the red nucleus and the vestibular nuclei with the vestibular nuclei and the lateral reticular spinal

tract and nucleus preserved. The dysfunction need not be structural since decerebrate states may occur with metabolic disturbances such as hypoglycemia, intoxications, or anoxia. If unilateral, the decerebrate postures are ipsilateral to the lesion.² Fragments of decerebrate postures have the same localizing significance as the fully developed decerebration.

Reflex withdrawal is most often seen in the lower extremities and is known as triple-flexion response, so named because it consists of flexion of the hip, knee and ankle. It represents withdrawal from a noxious stimulus and signifies involvement of the corticospinal tract. Babinski toe sign is probably part of this response. At times it is difficult to distinguish the reflex withdrawal from a voluntary withdrawal. The reflex withdrawal should be suspected, (a) when the movement occurs clearly only upon application of a noxious stimulus, (b) when the spontaneous movements are minimal or absent, and (c) when there is additional evidence of pyramidal tract deficit such as Babinski toe sign, or hyperreflexia of the affected limbs.

Tendon reflexes are usually depressed after an acutely occurring cerebral event that leads to coma. Thus for hours to days the stretch reflexes may be decreased on the paralyzed side. In the period of transition from hyporeflexia to hyperreflexia, one may find seemingly contradictory findings such as increased reflexes in the upper extremity and decreased reflexes in the lower.

Pathological reflexes, particularly the Babinski toe sign, have the same significance as in other neurological conditions affecting the pyramidal pathways and need no elaboration here. One must remember, however, that the Babinski toe sign may be absent or equivocal even though the corticospinal tracts are involved. Absent abdominal skin reflexes may further confirm pyramidal tract involvement.

Sensory System

A detailed sensory examination is usually not possible in a patient in a profoundly depressed state of consciousness, but the sensory system can be examined if the coma is not too deep and some responses are present. Facial expression of pain, restlessness and defensive movements elicited by noxious stimuli from one side only, indicate a hemisensory deficit, usually seen with large destructive lesions in the opposite hemisphere. Often the corneal reflex contralateral to the lesion will be decreased, indicating a sensory dysfunction. A diminished corneal reflex, however, could also indicate brain stem involvement.

CONCLUSION

The errors in the diagnosis of an unconscious patient are usually those of omissions either in history, examination, and laboratory studies, or in diagnostic formulations, which fail to consider all diagnostic possibilities. A systematic approach to evaluation should help in eliminating most of these errors. Nevertheless, there will be a small number of pa-

tients in whom a definitive diagnosis cannot be made while alive and in some not even on postmortem examination.

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Management of Urban Tetanus

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The problem of drug addiction has brought with it a resurgence of tetanus,⁷ a disease only recently on its way to extinction. When encountered in the drug addict, the disease almost invariably occurs in its severest form. The symptoms of tetanus may be masked in the narcotized patient or may be wrongly attributed to drug withdrawal. In both cases, therapy will be delayed and vital time lost.

Tetanus is diagnosed by the clinical picture, bacteriologic confirmation being rare. Trismus and/or paraspinal rigidity are the most common presenting symptom. These may remain localized when the disease is mild or may spread over hours or days in the moderate and severe forms, with superimposed, severe, generalized muscular spasms lasting seconds or minutes. The presence or absence of convulsions has been used as a basis for clarifying tetanus,¹⁸ as shown in Table 1. Conditions that must be considered in the differential diagnosis of tetanus are shown in Table 2.

Prior to the use of controlled ventilation, the majority of deaths were respiratory.^{2, 4} The introduction of controlled ventilation has reduced the number of deaths from respiratory causes. Cardiac disturbances are now the major mortality factor.^{12, 13, 15}

The following regimen is based on experience with 34 patients treated by a team from the Department of Neurology, Medicine, Anesthesiology, Nursing and Surgery at Harlem Hospital Center, and 14 patients treated by the Department of Medicine at the Kings County

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Table 1. *Grading of Tetanus*

MILD	MODERATE	SEVERE
Hyperirritability	Occasional generalized convulsions	Frequent generalized convulsions
Trismus		
Risus sardonicus		
Paraspinal muscle rigidity		
Opisthotonus		
No generalized convulsions		

Hospital from 1964 to 1971. Where modes of therapy differ between the two institutions, it is so stated.

IMMEDIATE MEASURES

Immediately after the diagnosis of tetanus is made, the patient should be transferred to an intensive care facility which has personnel trained in both respiratory care and cardiac resuscitation. The most immediate life-threatening condition in the early stages of tetanus is the development of a tetanic seizure and respiratory arrest. During the initial assessment of the patient, seizures can be immediately treated by keeping an intravenous line open at all times and administering succinylcholine (80 mg). Since paralysis follows administration of succinylcholine an oral airway, Ambu Bag, suction equipment, and oxygen must be available to ventilate the patient. This approach is most practical in the tetanus patient in whom oral trismus may delay orotracheal intubation, for it permits intubation and tracheostomy to be done as elective procedures—something to be desired when prolonged controlled respiration will be required.

WOUND MANAGEMENT

Immunotherapy and Wound Care

With provision having been made for any immediate respiratory emergency, management can next be focused on immunotherapy. Circulating toxin and toxin that is present in wound sites must be inactivated

Table 2. *Differential Diagnosis of Tetanus*

Drug reaction (phenothiazines)	Temporomandibular joint disease
Drug withdrawal	Hypocalcemic tetany
Meningitis	Retroperitoneal hemorrhage
Subarachnoid hemorrhage	Strychnine poisoning
Peritonsillar abscess	Decerebrate posturing
Epilepsy	

before further binding to tissue sites occurs. Six to ten thousand units of human tetanus immune globulin (Hu-Tet, Hyper-Tet) should be administered intramuscularly in the buttocks at the time of admission so that substantial circulating levels will be present when debridement is undertaken. Part of the immune globulin may also be infiltrated in the wound site.

Debridement may be performed 1 to 2 hours after administration of the immune globulin and institution of antibiotic therapy. Abscesses should be irrigated with hydrogen peroxide and necrotic tissue widely excised. Frequently in the addict, multiple small indurated pockets of infection are encountered which make extensive debridement impossible. Tetanus originating in puncture wounds is associated with a higher mortality.¹⁷ This, together with the difficulty of obtaining adequate debridement in the addict, may account for the high mortality in these patients.

The half life of immune globulin is 30 days, and thus it is necessary to initiate active immunization with tetanus toxoid for more permanent protection. During the first week, 0.5 cc. of alum-precipitated tetanus toxoid is given intramuscularly in a site distant from that used for the administration of immune globulin. Immune globulin activity is unaffected by toxoid, since the latter is slowly absorbed from the injection site. An additional 0.5 cc. is given again at 6 weeks and at 6 months. Infection with tetanus does not confer immunity against subsequent infection. Lasting active immunity is acquired only by administration of toxoid. In the nonimmunized individual, active immunity is demonstrable in the serum 7 to 10 days after the second injection.

Antibiotics

Clostridium tetani is sensitive to penicillin, which is the drug of choice for eradication of the organism. Ten million units daily has proven adequate in our experience. In individuals with penicillin allergy, tetracycline can be given intramuscularly every 4 hours in 500 mg. doses. Antibiotic therapy will not alter the course of the disease, which is basically a reflection of the toxin already bound to tissue sites. Only by eradicating the organism can further toxin production be prevented. An outline of antibiotic therapy in tetanus is included in Table 3.

MANAGEMENT OF VENTILATION

During the initial course of the disease, the major problem is usually one of ventilation. Muscular rigidity can impair pulmonary gas exchange by three mechanisms. First, oropharyngeal muscle involvement can prevent normal swallowing and cause not only obstruction of the upper airways by mucous secretions, but also aspiration of secretions. Second, tetanus frequently causes generalized rigidity of the muscles, distinct from tetanospasms limiting respiratory excursion, and leading to atelectasis with hypoxemia and even hypercarbia. Third, during tetanic convulsions, the chest wall becomes fixed in inspiration or expiration, ventilation ceases, and during this time mechanical ventilation is ineffectual until the tetanic muscles relax.

Table 3. *Program for the Treatment of Tetanus*

Immunotherapy	6000 to 10000 units of human tetanus immune globin IM Tetanus toxoid 0.5 cc. IM at 1 and 6 weeks and at 6 months
Antibiotic therapy	10 million units daily aqueous penicillin IV If penicillin allergy exists then tetracycline 500 mg. q 4 h IM
Wound care	Debridement 1 to 2 hours following initial antibiotic therapy and immunotherapy Exposure of wounds to hydrogen peroxide
Muscle relaxation	Sodium luminal, 100 to 200 mg. IV or IM q 3-4 h plus Chlorpromazine hydrochloride, 75 to 100 IM q 3-4 h Morphine sulfate, 5-35 mg. IV or IM q 3-4 h Paraldehyde, 2.5 cc. IM prn Diazepam, 10 mg. IV q 1-3 h prn Curare, 9 to 15 mg. IV over 10 minutes every hour for intractable spasms Succinylcholine for emergency in intractable spasm, not for maintenance If morphine not used, methadone 10 to 15 mg. IM q 4 h to prevent narcotic withdrawal
Respiratory management	Tracheostomy for all but mild tetanus Intermittent positive pressure breathing with a volume-cycled respirator

Table 4. *Tracheal and Respiratory Care Requirements*

An intensive care unit with nurses trained in respiratory care
Monitor respirator pressure q 1/2 h, minute ventilation q 1 h, and blood gases bid
Rotation of the patient from side to side q 2 h and chest percussion bid
Frequent suctioning using disposable gloves and sterile catheters
Tracheal culturing twice a week
Frequent sterilization of respirators
Leaving initial tracheal cannula in until a tract has been established and then changing cannulas every 48 hours
Use flexible tracheostomy tubes and low pressure cuff balloons

We have never encountered mild tetanus in drug addicts. The apparent initial mild symptomatology in these patients has, in our experience, been in reality moderate or severe tetanus masked by the addicting drugs. For this reason, we feel that early tracheostomy is indicated in every drug addict presenting with tetanus. Additional indications for tracheostomy are inability to effectively clear oropharyngeal secretions and a decrease in arterial oxygen saturation below 90 per cent, an arterial Po_2 less than 70 mm. Hg, or an arterial PCO_2 greater than 50 mm. Hg owing to muscle spasm. Long term mechanical ventilation requires meticulous tracheal toileting if the complications of tracheostomy are to be avoided. Some of the more important points in such care are outlined in Table 4.

Arterial blood gases should be monitored at least twice daily and more often if necessary. Continuous monitoring of minute ventilation is desirable, but where this cannot be done then at least hourly monitoring should be obtained. Monitoring of respiratory pressures can be an excellent guide to early changes in the respiratory system.

The total pressure generated by the respirator during a respiratory cycle will be a sum of the pressures required to overcome airway resistance, to inflate the lung, and to overcome chest and abdominal wall resistance. An increasing pressure requirement to deliver the same volume will signal the need for suctioning of secretions which increase airway resistance, for periodic hyperinflation to correct low lung compliance related to atelectasis, or for increased muscle relaxation because of increasing chest and abdominal wall rigidity. Variation in the latter imposes the requirement that only volume-cycled respirators be used, to insure delivery of constant volumes.

Numerous sedatives have been recommended to control the often lethal tetanospasms; these include barbiturates,⁵ chlorpromazine,¹ paraldehyde,⁹ mephenesin,¹ chloral hydrate,¹³ diazepam,³ and morphine.⁶ Our own clinical experience supports our impression that no one sedative or combination is preferable to any other. At Kings County Hospital it has been usual to begin with morphine sulfate, 5 to 35 mg., plus phenobarbital, 50 to 200 mg. intramuscularly or intravenously every 3 to 4 hours. At Harlem Hospital, phenobarbital plus chlorpromazine, 75 to 100 mg., are the usual initial agents, with methadone, 10 to 15 mg. every 4 to 6 hours, given to addicts. If spasms continue despite maximal doses of these agents, paraldehyde or diazepam is added as described in Table 3.

If spasms still persist, the patient is curarized,⁸ using the lowest dose necessary to abolish spasms, usually around 9 to 15 mg. given intravenously over 10 minutes every hour, with gradual tapering over the next days or weeks. The usual duration of such therapy is 2-3 weeks. Higher doses of curare can cause hypotension; we continue one or two of the above sedatives in curarized patients in order to use minimal curare doses, and also to depress the patient's level of awareness.

The advantage of curare is that it permits total muscle relaxation. The disadvantages are that coughing is abolished and the patient cannot respond should mechanical failure of the respirator occur. Vigorous postural drainage and suctioning and extremely close observations are therefore essential, plus physical therapy to prevent contractures of the muscles.

CARDIAC MANAGEMENT

Sudden cardiac standstill is currently the major cause of death in tetanus in this country, occurring during the second or third week in the course of the disease. The mechanism is not well understood. Blood gases are usually normal, and so hypoxemia and acid-base disturbance cannot be implicated. While tachycardia and bradycardia are frequently encountered, other electrocardiographic changes are less common. Blood pressure shows marked lability, with extremes of both hypertension and hypotension.

Three types of arrest have been encountered. First and most frequent is sudden electrical asystole. The only premonitory sign is sudden marked blood pressure lability shortly before the arrest. This type usually responds very rapidly to usual resuscitative measure of external cardiac massage and intracardiac instillation of 2 ml. of 1:10,000 epinephrine and 4 ml. of 10 per cent calcium chloride. Second and relatively rare is ventricular fibrillation, which usually occurs only in the presence of hypoxemia. Third and not infrequent is sudden mechanical asystole with continued normal electrical systole. This type of cardiac disturbance responds poorly to all resuscitative measures. Attempts to prevent asystole by the use of cardiac pacemakers have been unsuccessful.

Elevated catecholamine levels have been demonstrated during the acute phase of tetanus, and it has been postulated that the cardiac arrest of tetanus may be the result of prolonged exposure of the heart to these catecholamines.^{11, 12} Some workers have advocated the use of alpha and/or beta adrenergic blocking agents.¹¹ At Kings County Hospital propranolol has been given via nasogastric tube in doses of 10 mg. four times daily to patients in whom the cardiac rate remains persistently above 100 beats per minute. At Harlem Hospital, on the other hand, those patients who arrested without hypoxia at the time have all showed either sudden cardiac standstill or bradycardia progressing to a standstill. Propranolol has therefore not been used, pending the availability of more data as to its efficacy. Other measures to be observed in cardiac management are shown in Table 5.

Table 5. *Cardiovascular Management in Tetanus*

ABNORMALITY	PREVENTION AND THERAPY
Blood pressure lability	Adequate daily fluid replacement
Tachycardias	Maintenance of normal blood gases
	Minimize respirator inspiratory time
	Maintain normal electrolyte and acid-base balance
	Investigate for infection, embolism, hemorrhage
	Optional: Give propranolol, 10 mg. qid via nasogastric tube for persistent cardiac rates over 100 beats per minute
Bradycardia	Minimize reflex vagal stimulation (avoid prolonged suctioning and monitor EKG during suctioning)

METABOLIC MANAGEMENT

Perhaps related to the elevated catecholamines, tetanus is associated with a hypermetabolism that may require up to 7000 calories daily. A 30 lb. weight loss during the 3 weeks of the acute phase of the disease is not infrequent when the caloric demands cannot be met. Routine parenteral therapy is insufficient to meet these needs, and at Harlem Hospital hyperalimentation via a subclavian catheter has been used, as described elsewhere.¹⁶ At Kings County Hospital the patient has usually received intravenous glucose during the first week and then nasogastric tube feedings have been added during the subsequent course. Vitamins, especially thiamine, vitamin C and vitamin K, iron, calcium, and magnesium are included. Conventional tracheal tube cuffs require periodic deflation to prevent tracheal pressure necrosis, and carried with it the risk of aspiration. This hazard has been avoided by the use of intravenous hyperalimentation. Newer pressure cuffs, where they are available, allow prolonged inflation and thus minimize the possibility of aspiration, making practical the use of nasogastric feeding. Metabolic requirements can be met, and gastrointestinal bleeding can be prevented and monitored.

MANAGEMENT OF OTHER COMMONLY ENCOUNTERED PROBLEMS

Hyperthermia is common during the acute course of tetanus, related both to the presence of infection and to the severity of tetanic muscle contractions. The temperature in one of our patients rose to 109° F. Hyperthermia has responded dramatically to adequate muscle relaxation, and heat dissipation has been facilitated by the use of a combination of 50 mg. of meperidine, 25 mg. of thorazine, and 25 mg. of phenergan given intravenously. Even in the absence of hyperthermia, periodic profuse sweating is common and insensible water loss can be considerable, causing dehydration and contributing to hyperthermia.

The sudden spasmodic convulsions of tetanic muscle require that all pharmacologic agents be delivered via a central venous line and that the line be checked for location of the catheter tip if such agents fail to produce an effect. A sudden tetanic convulsion can force the catheter tip through the vessel wall, making delivery of relaxant agents ineffectual.

Gastrointestinal bleeding is common in patients receiving mechanical ventilation via tracheostomies. Lower gastrointestinal tract bleeding may be secondary to fecal impaction, and it is useful to clear the intestine with suppository laxatives. Upper gastrointestinal tract bleeding is a more serious problem, and we have attempted to prevent it by giving milk and antacids via nasogastric tube. Hypoprothrombinemia may be seen if vitamin K is not routinely included in the patient's therapeutic regimen.

Myopathy in tetanus has only recently been recognized, but may play an important role during the recovery phase. The toxin produces muscle damage during the first 2 to 3 weeks of the disease, often leaving a patient with marked weakness of both respiratory and peripheral mus-

cles. The cough reflex may be ineffective, and the patient can easily asphyxiate from sudden airway obstruction by a mucous plug. Thus the transition from mechanical to self-sustained ventilation must be made slowly during the recovery phase, with the patient initially off the respirator for short periods of 15 to 30 minutes in the daytime, this time interval being gradually increased using arterial blood gas and force vital capacity measurements as guidelines for the rate of weaning from the respirator. The arterial Po_2 should be above 60 mm. Hg on room air with a normal arterial Pco_2 , and the patient must have a vital capacity which is three times his predicted normal tidal volume before one considers complete cessation of mechanical ventilation.

Metabolic alkalosis has been encountered during the third to fourth week of the disease in some of our patients. If urinary electrolytes are monitored, one finds progressively decreasing sodium concentrations and increasing potassium concentrations. The alkalosis is readily reversed with spironolactone. This effect suggests that hyperaldosteronism is responsible for the metabolic alkalosis. A causal relationship between alkalosis and cardiac arrhythmias has been demonstrated in other clinical conditions, and the additive effect of hypokalemia to muscles already functionally impaired by tetanus and/or prolonged paralysis can further endanger respiration and prolong recovery.

Our patients have been relatively young, and perhaps for this reason thromboembolism has been rare. It is more common in series reporting on tetanus in the non-addict population, and some authors have recommended routine anticoagulation therapy.¹²

Other problems that have been reported in tetanus include hyperglycemia with and without ketosis, the latter being unresponsive to insulin therapy; anemia, which has not been well studied but which is associated with a shortened red cell survival; hypoalbuminemia, which has been attributed to the marked negative caloric balance that results in many of these patients; paralytic ileus and tracheal stenosis, sometimes occurring several weeks after a tracheostomy has closed.

In conclusion, tetanus challenges the skills of several disciplines, including neuropharmacology, respiratory physiology, cardiology, physiotherapy, and intensive care nursing, and a team approach is the best assurance of a successful outcome.

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Infective Endocarditis Today

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Bacterial infection of the valvular and mural endocardium has been of special interest to clinicians in the municipal hospital setting for many years. As a diagnostic dilemma, endocarditis has provided any number of isolated case reports and clinicopathologic exercises. Though the clinical picture so well described in authoritative tracts and texts continues to be seen in municipal institutions, social change and increasing numbers of urban patients using unsterile drugs intravenously has changed the pattern of endocarditis. The exact incidence of this disease is difficult to establish; however, bacterial endocarditis has been said to rank behind coronary, hypertensive, and rheumatic heart disease.²³ On the wards of the Bellevue Hospital of the New York University Medical Center the incidence of bacterial endocarditis has approached or surpassed that of rheumatic heart disease.

The classification or separation of the disease into acute and subacute varieties on the basis of infecting organism has not proved to be as valid as previously cited. We have had experience with instances of clinically acute disease caused by organisms conventionally thought to be "low-grade" or nonpathogenic, and instances of virulent pathogens producing subacute disease (*Staphylococcus aureus*, a common cause of acute bacterial endocarditis,²⁷ has on occasion produced the clinical picture of subacute disease²²). We shall refer to both acute and subacute entities as bacterial endocarditis. Whatever may be the usual pathogenicity of the organism causing acute fulminant bacterial endocarditis, rapid diagnosis and early initiation of therapy frequently make the difference between survival and death. Thus, despite these changes which have become apparent since the availability of penicillin, the clinical classification of endocarditis as acute and subacute remains both valid and important.^{27, 28}

ETIOLOGY (INCITING ORGANISM)

Streptococci (viridans, enterococci, microaerophilic) and staphylococci have been cited as being the causative agents in 90 per cent of cases

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of bacterial endocarditis.³⁶ Of particular interest is the relatively high frequency with which Lancefield Group "H" streptococci are found in cases of bacterial endocarditis among rheumatic patients on penicillin prophylaxis.⁴ Hemolytic activity may be a deceptive characteristic: strains of Group "D" streptococci (enterococci) can produce beta (complete), alpha (green), or gamma (no) hemolysis, necessitating further confirmatory studies (e.g., growth in 6.5 per cent NaCl and 0.1 per cent methylene blue) for identification. Errors made by relying on the capacity to hemolyze can be of great significance, since the therapy for endocarditis caused by viridans streptococci and strains of beta hemolytic streptococci (e.g., Groups A, B, C, F, G, H) is inadequate to cure enterococcal disease. It is also noteworthy that the enterococcus behaves clinically like the pyogenic cocci (staphylococci and pneumococci) in its capacity to produce abscesses and tissue destruction.²⁸ It has been our experience that this has also been true for the Lancefield Group "H" streptococci. Enterococci, however, like the pyogens, have been noted to affect normal valves.

Enterococcal infections commonly result from bacteremia following genitourinary manipulation in males, or following abortion or childbirth in females.²¹ *Streptococcus viridans* bacteremia occurs most often after oral or dental manipulation, sometimes even minimal manipulation.²⁴ Atypical bacterial forms (streptococcal "L" forms or protoplasts) have been isolated from the valves of patients undergoing prosthetic valve replacement following successful penicillin treatment for bacterial endocarditis. This suggests that employment of hypertonic media routinely in obtaining blood cultures may prove to be effective in increasing the yield of positive blood cultures in clinically apparent cases of bacterial endocarditis.

Staphylococcal infections have become increasingly prevalent with the widespread practice of long-term administration of intravenous drugs in hospital therapy, and as a complication of the intravenous use of unsterile heroin.²² *Staphylococcus aureus* is a major problem among heroin addicts, with disease occurring for the most part on normal valves.^{3, 25} The alarming incidence of *Staphylococcus aureus* endocarditis after open heart procedures, noted in the early days of open heart surgery, has decreased with the common practice of using prophylactic anti-staphylococcal agents. *Staphylococcus albus*, however, commonly considered a nonpathogen and frequently discarded as a "contaminant" in the interpretation of blood cultures, is a common offender in such cases.^{11, 30} To compound the difficulties, these organisms are frequently resistant to the semisynthetic penicillins conventionally used as prophylactic agents.

Other Microorganisms

The pneumococcus and gonococcus, once prominently associated with endocarditis,^{19, 35} are infrequently seen as offending agents. The current epidemic of gonorrhea, however, requires that one be aware of the potential resurgence of gonococcal endocarditis.

Gram Negative Infections

The coliform organisms have infrequently been associated with bacterial endocarditis other than among "main line" narcotic addicts and patients who have had open heart prosthetic valve surgery. In these situations strains of *Enterobacter* sp., *Klebsiella* sp., and *Pseudomonas* sp. have been isolated.^{8, 10} *Salmonella* bacteremia complicated by bacterial endocarditis is fortunately rare, for it has an extremely poor prognosis and is usually fatal despite heroic therapeutic efforts.⁴

Unusual Organisms

A wide variety of bacterial and rickettsial organisms have been reported to cause bacterial endocarditis. We have experienced instances of endocarditis with *Listeria monocytogenes*, *Hemophilus aphrophilus*, *Corynebacterium acnes*, *Serratia marcescens*, and *Salmonella enteritidis*. The majority of such patients were found to be severely debilitated as a result of other disease, were on immunosuppression therapy, or were "main line" drug addicts.

Mycotic Infections

Fungal endocarditis in the urban center occurs almost exclusively in drug addicts, in patients following open heart operation, and less commonly in patients on long-term indwelling venous catheters receiving either antibiotic or hyperalimentation therapy.^{27, 33, 34}

CLINICAL PICTURE

Acute bacterial endocarditis often presents with an extensive primary lesion (e.g., cellulitis, osteomyelitis, pneumonitis). If the primary focus is active at the time of presentation both infections contribute to the clinical picture. The endocardial infection may in such instances be overshadowed by the primary lesion. The following case presentation from the wards of New York University-Bellevue Medical Center illustrates this point.

A 30 year old man, a known heroin addict, was admitted to the surgical service of Bellevue Hospital with symptoms of nausea, vomiting, diarrhea, fever, and an abscess of the left forearm. Physical examination revealed an acutely ill white man in moderate respiratory distress. Blood pressure was 110 mm. Hg systolic, 70 diastolic. Pulse, 96; temperature, 105°F; respiration 28 and regular. HEENT unremarkable. Chest revealed decreased percussion note, tactile fremitus and breath sounds over the right posterior lung field. Course rales were heard over the right lateral chest and at the left mid lung field posteriorly. Heart was not clinically enlarged. A high pitched grade II/VI systolic murmur was heard at the apex which radiated to the left sternal border. Abdomen revealed a mildly tender liver palpable 2 to 5 cm. below the right costal margin in the mid clavicular line. No spleen was felt. Extremities revealed no clubbing. There was a fluctuant abscess of the left forearm.

Laboratory findings: WBC = 22,000 P = 83 L = 9 M = 1 Hct. = 43% Creat. = 1.2 mg% BS = 96 mg% LFT = within normal limits. Urine = pH 6 SG = 1.021 Glucose, Acetone = Neg. Prot. = 2+ Micro = WBC = 2-10/HPF RBC = 0 Gram stain of sputum: gram positive cocci in clusters and pairs with many

polymorphonuclear cells. Gram stain of abscess: gram positive cocci in clusters. Cultures of the sputum, abscess, and blood revealed *Staphylococcus aureus*, coagulase and mannite positive. The chest x-ray (Fig. 1A) revealed patchy areas of increased density in the right upper lobe with radiolucent centers suggestive of cavitation, and blunting of the right costophrenic angle.

The patient was transferred to the medical service with the pulmonary process now involving both lungs (Fig. 1B), and was started on oxacillin therapy, 4 gm. intravenously every 6 hours. A presumptive diagnosis of acute bacterial endocarditis with multiple infected pulmonary infarcts and secondary abscess formation was made. The patient responded to a six-week course of therapy and was discharged on a methadone program without evidence of congestive failure.

Symptoms in subacute bacterial endocarditis are due to endocardial involvement and its complications. The primary focus of infection is usually undetermined other than by history. Symptoms are usually variable, being characterized by gradual onset. Lassitude, weakness, low grade fever, easy fatigability, vague abdominal or lumbar pain, and weight loss are common causes for presentation to a physician. The protracted nature of the diseases frequently causes confusion. The consideration of "a viral syndrome" with administration of an antibiotic for lack of a better course of action is commonplace. On the other hand, the presence of a history of cardiac disease, chills, fever, anemia, cardiac symptoms, or findings of microembolic phenomena, splenomegaly, joint pains, and recent history of manipulative procedure (oral or genital) usually prompts consideration of the diagnosis and results in early hospitalization.

ORGAN SYSTEMS INVOLVED

SKIN. The skin and mucous membranes are commonly affected with five characteristic lesions that are valuable in diagnosis:

1. Petechiae with and without central clearing can frequently be found in the palpebral conjunctiva, the fundus, in the skin of the shoulders (above the clavicles), and on the dorsum, plantar, and palmar surfaces of the extremities. The oral mucous membranes may be involved, particularly the hard and soft palate and sublingual areas. Petechiae, however, are not pathognomonic of bacterial endocarditis and can be found in a variety of other conditions.

2. Splinter hemorrhages, the linear hemorrhagic streaks that appear under the nails, occur in a variety of conditions and are most commonly the result of local trauma.⁷

3. Janeway lesions are small macular or papular lesions, one to four millimeters in diameter, which occur most often on the palms, the soles, or on the tips of the fingers and toes. They characteristically blanch with pressure and are never painful.^{15, 23}

4. Osler's nodes are small, erythematous, pea-sized, tender lesions which occur most frequently on the tips of fingers and toes, on the plantar surface of the feet and palmar surface of the hands, or along the sides of the fingers and/or toes. These lesions (pathognomonic of bacterial endocarditis) are always tender and are distinguishable from the Janeway



Figure 1. Acute bacterial endocarditis with multiple infected pulmonary infarcts and secondary abscess formation. The chest x-ray shows patchy areas of increased density in the right upper lobe with radiolucent centers suggestive of cavitation, and blunting of the right costophrenic angle. *B*, Later the pulmonary process is seen to involve both lungs.

lesions by this fact. They may be ephemeral, lasting from hours to several days.^{23, 26}

5. Clubbing, a sign noted in the course of examining the skin and appendages, occurs in 12 to 52 per cent of patients with endocarditis and tends to recede with treatment and cure.³

HEART. The presence of murmurs indicating previous organic heart disease is of diagnostic significance. Changing murmurs indicating intracardiac damage in the form of valvular vegetations, chordae tendineae rupture, or valve perforation may occur.³²

Disturbances of conduction are relatively uncommon when compared to active rheumatic fever, but arrhythmias from premature contraction to auricular flutter, and conduction abnormalities from prolonged PR interval to complete heart block have been described.²⁹

Pericarditis may occur as a result of coronary embolism or subpericardial infarction, or secondary to perforation of a mycotic aneurysm. Cardiac failure often occurs late in the course as an expression of myocardial damage or as a result of acute catastrophe (i.e., perforation of a valve cusp).

SPLEEN. Splenomegaly occurs in 28 to 57 per cent of patients³⁷ and may be associated with pain resulting from infarction. A palpable or audible friction rub may be found.

GENITOURINARY SYSTEMS. The genitourinary system is most often affected by microemboli. Occasionally gross hematuria may occur; however, as a rule only microscopic hematuria occurs, accompanied by albuminuria. The degree of albuminuria however, depends upon the presence and extent of glomerular involvement. Glomerular involvement may occur as a result of diffuse proliferative glomerulonephritis or secondary to focal embolic lesions in the so-called "flea-bitten kidney."³ These conditions are usually associated with some degree of renal insufficiency. The presence of a moderate degree of azotemia may also occur in the presence of heart failure independent of renal insufficiency.

LUNG. Pulmonary findings are uncommon unless endocardial vegetations occur on the right side of the heart, as in cases of congenital heart disease, tricuspid involvement (drug related), or when patent foramen ovale, ventricular septal defect, or patent ductus arteriosus exists.^{1, 2}

GASTROINTESTINAL TRACT. The gastrointestinal symptoms are usually an expression of congestion of the circulation with occasional involvement of viscera as a result of embolization and infarction. The spleen, kidney, and intestinal tract may be involved.²⁸

JOINTS AND BONE. Arthralgia and occasionally true arthritis with joint swelling may occur. Back pain with localization to the sacrum, ischium, and other bony sites has been ascribed to periostitis.²³

BLOOD. Anemia secondary to infection is quite characteristic of the disease.^{2, 3} The white cell count is variable, often being normal or very slightly elevated. Extreme elevations of the white blood count and persistently elevated counts usually herald a complication (e.g., organ infarct, mycotic aneurysm, or abscess). Leukopenia may also occur.

Histiocytes in earlobe specimens have been described in bacterial endocarditis.⁶ They can be seen, however, in bacteremia from other causes

and in normal persons to a lesser degree. Purpura and bleeding diathesis have been described, affecting primarily the lower extremities, although epistaxis occurs in 3 to 4 per cent of cases.¹² This hemorrhagic process probably represents unrecognized diffuse intravascular coagulation. Rheumatoid factor, occurring in the serum of 50 per cent of patients with bacterial endocarditis, has been described to decrease or disappear after successful treatment.⁴⁰

CENTRAL NERVOUS SYSTEM. Vascular lesions of the central nervous system are common. These include mycotic aneurysms, bacterial microemboli, and arteritis, resulting in intracerebral hemorrhage, subarachnoid hemorrhage, and/or encephalomalacia.^{27, 28} Symptoms include headache, change in sensorium, confusion, meningeal signs, focal neurologic signs, somnolence, coma, and death.

EYE. Conjunctival petechial hemorrhages and retinal hemorrhages are often seen and are important diagnostically. These retinal lesions are described as boat-shaped petechiae and flame-shaped hemorrhages with central clearing. The Roth spot, a reaction of hypersensitivity described pathologically as an accumulation of lymphocytes in the nerve fiber surrounded by edema and hemorrhage, is rarely seen.¹⁹ Optic neuritis, embolism of the central retinal artery, and embolism of the cilioretinal artery has been described. These are accompanied by varying degrees of vision loss.

DIAGNOSIS

The clinical diagnosis of bacterial endocarditis rests with the presence of an acquired valvular, or appropriate congenital lesion as a seat for disease, fever, and microembolic phenomena. The diagnosis is supported by the findings of one or more positive blood cultures. The absence of a positive blood culture does not exclude the diagnosis; some 7 to 28 per cent of instances of bacterial endocarditis may occur with negative blood cultures.^{9, 22} A single positive streptococcal blood culture in the absence of other findings does not, however, indicate the presence of bacterial endocarditis, since transient bacteremia may occur in the absence of significant disease.

Because of the multiplicity of systems involved and the variety of symptoms associated with this entity, a large number of diseases must be considered in the differential diagnosis.

Early in the course the general symptoms of fever, fatigue, vague pain, dyspnea, and cough may be mistaken for influenza or pneumonia. Prolonged fever and splenomegaly may be mistaken for such diseases as malaria, typhoid fever, or brucellosis. These diseases can usually be distinguished by blood cultures, serologic studies, stool and urine cultures, and examination of thick and thin blood smears for parasites. Lymphoma is to be considered in a setting of fever of undetermined origin and splenomegaly. In general, however, the lymphadenopathy seen in lymphomas will distinguish this condition from bacterial endocarditis.

Rheumatic fever may mimic bacterial endocarditis. The typical migratory polyarthritis, erythema marginatum, subcutaneous nodules, and marked conduction disturbances serve as features that separate acute rheumatic fever from the microembolic phenomena, splenomegaly, Osler's nodes, Janeway lesions, clubbed fingers, and positive blood cultures of bacterial endocarditis.

Hyperthyroidism might be considered in a patient with weight loss, easy fatigability, nervousness, and fever. The determination of serum thyroxine level should eliminate this consideration. Diffuse proliferative glomerulonephritis with hematuria, albuminuria, and progressive renal insufficiency is seen in bacterial endocarditis, but can be distinguished clinically from post-streptococcal glomerulonephritis by the absence of hypertension.²²

Primary cerebral or meningeal findings may predominate and lead to diagnostic confusion. Examination of the cerebral spinal fluid and search for other evidence of bacterial endocarditis will usually clarify the diagnosis.

The patient subject to open heart surgery will commonly run a febrile course following operation. The length of the uncomplicated febrile period is usually 4 to 10 days. Fever occurring in patients beyond this time requires consideration of bacterial endocarditis. Since the characteristic features of infectious endocarditis are often absent following cardiac surgery,²² two major syndromes included in the appropriate differential diagnosis are:

1. *The post-pericardiotomy syndrome*, which usually occurs from two weeks to six months after surgery, with signs of fever and symptoms of pleuritis, pericarditis, arthralgia, and myalgia. The laboratory findings reveal leukocytosis, elevated erythrocyte sedimentation rate, and negative blood cultures.

2. *The post-perfusion syndrome*, with fever, splenomegaly, lymphadenopathy, and atypical lymphocytes in the bloodstream, occurs 3 to 4 weeks post operation. Characteristically the well being of these patients is remarkable when compared to the patient with endocarditis. Major complaints, usually relating to fever, disappear with the onset of the afebrile state.

Neither of these two conditions requires antibiotic therapy. Both tend to be self-limited.²⁰

TREATMENT

A specific bacterial diagnosis is crucial for the choice of appropriate therapy of bacterial endocarditis, and effective antibiotic therapy is crucial for recovery. Although a variety of therapeutic regimens have been proposed, the consequence of therapeutic failure is such that antibiotic dose, route of administration, and duration of treatment must be optimal.

Patients with bacterial endocarditis should be treated in a hospital

with effective bacteriologic facilities with the understanding that they will spend 6 or more weeks in hospital.

Antibiotic therapy is determined on the basis of sensitivity of the causative agent. Bactericidal agents—the penicillins, cephalosporins, streptomycin, and vancomycin—are the agents of choice.¹³ Recommended therapy for sensitive streptococcal disease is parenteral (preferably intravenous) penicillin therapy for at least 4 to 6 weeks. Initial penicillin therapy is started at 15 to 20 million units per day administered intravenously in divided dosage. The therapeutic dosage is adjusted thereafter to produce serum dilution bactericidal levels of 1/16 or better.¹⁶

The presence of a history of penicillin allergy has in our experience most often proven to be inaccurate. However, the ability to perform allergy testing with the polylysine penicilloyl derivative, to determine the patient's allergic status accurately, and allow for safe administration, is needed.³⁸ Desensitization in the presence of major determinant allergy has been accomplished where penicillin therapy is considered to be absolutely necessary (i.e., relapse in the face of other therapy). Cephalosporins should be used with caution in patients with penicillin allergy, since cross-reactions may occur. Vancomycin, an effective bactericidal agent, should be monitored for renal and marrow toxicity. On occasion one may be obliged to use the bacteriostatic agents lincomycin, erythromycin, or tetracycline. These agents have been used with success but are not recommended as optimal therapy for bacterial endocarditis.

Enterococcal endocarditis and endocarditis caused by relatively resistant streptococci should be treated with intravenous penicillin, coupled with streptomycin, for a period of 4 or more weeks. We have recently added streptomycin to our regimen in the treatment of endocarditis caused by sensitive streptococci because of the isolation of "L" forms from the valves of patients undergoing open heart surgery after apparent successful penicillin therapy.

Staphylococcal endocarditis should be treated with comparable doses of intravenous penicillin G in the case of penicillin sensitive organisms, or a semisynthetic penicillin (oxacillin or methicillin) in penicillinase-producing strains. The usual dose range in the adult patient, 12 to 16 gm. per day, is administered intravenously in divided dose. In the presence of penicillin allergy cephalothin or lincomycin are suitable substitutes, with the above noted cautions. Uncommon bacterial agents are treated with agents selected on the basis of *in vitro* determination of drug sensitivity.

Surgical therapy is most often predicated on hemodynamic indications. On occasion inability to control or eradicate infection medically (e.g., fungal infection) has fostered surgical intervention, with limited success.^{18, 39}

Recovery from infective endocarditis was unusual before the availability of effective antimicrobial agents. The development of penicillin and the newer antimicrobials, bolstered by advances in cardiac surgery, has vastly improved the outlook for cure. Attempts to shorten the course of therapy or alter the mode of administration of antimicrobials is in our view unwise; relapses still occur in 7 per cent of patients.

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Acute Forms of Tuberculosis

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During the past 20 years the successful use of isoniazid and other drugs has demonstrated that tuberculosis is usually curable. In the acute forms, early diagnosis is imperative if therapy is to be effective.

The absolute diagnosis of tuberculosis requires bacteriologic confirmation. Other diagnostic aids are presumptive, including demonstration of organisms by stained smears of body exudates or histologic patterns in biopsied tissues. Both abnormalities can be mimicked by other diseases which will not respond to anti-tuberculosis therapy. The clinician is handicapped because the tubercle bacillus requires 4 to 8 weeks to be identified in culture. Most patients with acute tuberculosis cannot wait this long. In the majority of situations treatment must be initiated utilizing available clinical and laboratory aids, in as much as the diagnosis is presumptive. Every effort should be made before treatment is started to obtain a maximum of clinical and bacteriologic data. The doctor should be thorough but quick. The sputum specimen must be carefully collected by the physician after instructing the patient. Without such instruction and observation, the laboratory may receive a saliva specimen or gargled water.

It is often necessary to start treatment without proof of diagnosis. A desperately ill patient whose illness is strongly suggestive of tuberculosis merits intensive and continuous treatment—not a “therapeutic trial.” Simply adding isoniazid to a medley of antibiotics leads to confusion and disaster.

SPECIAL PROBLEMS

Acute Tuberculous Pneumonia

Tuberculosis on rare occasion presents as an acute pneumonic process ushered in by typical symptoms of pneumonia with chills, chest pain, prostration, tachycardia, and high fever. Since the process is lobular

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or lobar in extent, it evokes on physical examination findings of consolidation (bronchial breath sounds, bronchophony, rales). Pathologically consolidation is followed shortly by caseation necrosis; roentgenographically this produces characteristics of necrotizing pneumonia. The sputum may be purulent, and there may be a peripheral leukocytosis. The following case illustrates the similarity with nontuberculous suppurative disease, such as gram-negative bacillary pneumonia.

A.M., a 61 year old black woman with a history of chronic alcoholism was admitted to Harlem Hospital with chief complaints of fever, chills, and cough for 1 week and diaphoresis and hemoptysis of 2 days' duration. The patient had been well all her life until a week before admission when she noted a cough productive of large quantities of yellow sputum, malaise, and fever. During the week before admission she had increased malaise, nausea, and a few vomiting episodes. Two days before admission, she noted that she was coughing up clots and specks of blood mixed with brownish yellow sputum. She denied any history of chest pain, tuberculosis or exposure to it, leg pain, dyspnea, cardiac disease or episodes of unconsciousness. She was not under medical treatment, but a routine chest x-ray one month before admission was normal.

The temperature was 103°, the pulse 125, and respirations 25. The blood pressure was 140 mm. Hg systolic, 90 diastolic. Physical examination revealed an anxious, diaphoretic, acutely ill woman in moderate respiratory distress. There were scattered rales and ronchi over the right anterior and posterior chest. The hematocrit was 42 per cent. The white cell count was 4200, with normal differential distribution. Urinalysis was unremarkable save for 2+ albuminuria.

Initial sputum examination showed gram-positive cocci in chains, clumps, and pairs, with many polymorphonuclear leukocytes. X-ray examination of the chest on the day of admission showed a normal heart shadow, but there was 5 cm. diameter cavitory lesion in the posterior segment of the right upper lobe with diffuse fluffy infiltrates of the right upper and middle lobes (see Fig. 1). The intermediate PPD skin test was 5 mm. induration at 48 hours. The electrocardiogram was normal.

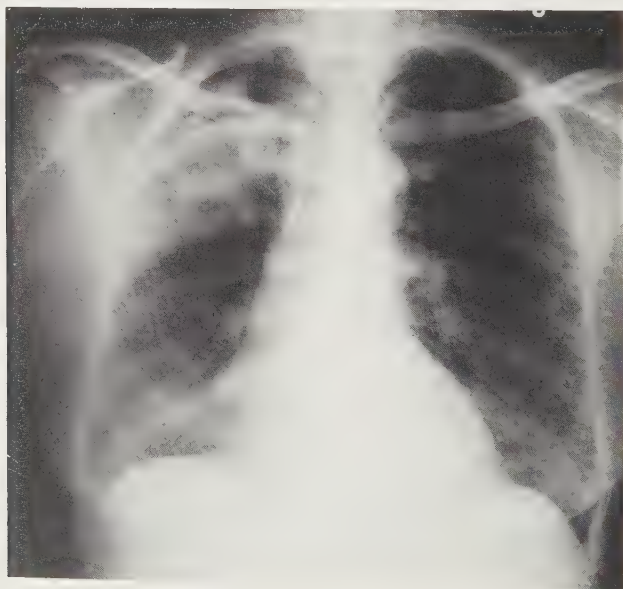


Figure 1. Right lung infiltration with upper lobe abscess and middle and lower lobe infiltrates.

The patient was treated with aqueous penicillin, 500,000 units intravenously every 6 hours starting on the first hospital day. On the sixth hospital day, her temperature was still spiking to 104°. Sputum gram stain revealed many polymorphonuclear leukocytes, a few gram-negative rods, and gram-positive cocci in clusters. The acid-fast stain was again negative. Sputum cultures taken on admission were growing out *Streptococcus viridans*, *E. Coli*, and *Staphylococcus aureus*. Blood cultures grew out no organisms. The antibiotic regimen was changed to gentamycin, 90 mg. intramuscularly every 8 hours. On the fourteenth hospital day, the patient was still febrile. Two sputum smears at this time revealed acid-fast bacilli. The patient was started on antituberculosis therapy with subsequent improvement in her clinical state, confirmed by clearing of the chest x-ray.

This case of necrotizing pneumonia in an elderly alcoholic woman with acute onset of illness illustrates how closely tuberculous pneumonia may imitate other acute bacterial pneumonias in both clinical and roentgenographic features. It demonstrates the importance of careful and repeated examination of sputum smear for acid-fast bacilli. In the patient incapable of producing sputum it may be necessary to obtain a specimen by inducing cough or tracheal aspiration. The tuberculin skin test will yield a positive reaction in most instances, but may be temporarily suppressed.⁸ The demonstration of reactivity on lymphocyte transformation study may be of value in the latter.¹⁴ Definitive diagnosis will require cultural identification of *Mycobacterium tuberculosis*.

Miliary Tuberculosis

Miliary tuberculosis represents blood-borne dissemination of tubercle bacilli. This presents clinically as an acute or subacute febrile illness and roentgenographically as multiple discrete nodules scattered uniformly throughout both lung fields. In the pre-chemotherapy era this form of tuberculosis was frequent in young children; today the disease is encountered with increasing frequency in older persons.⁶ Dissemination does not occur in patients under antituberculosis therapy.

The disease must be considered in every case of fever of undetermined origin; moreover it is important to remember that as an opportunistic infection, tuberculosis may complicate those conditions associated with compromised host defense mechanisms. Of importance among the latter are diabetes mellitus, chronic alcoholism, the leukemias and lymphomas, and patients receiving corticosteroids, cytotoxic, and immunosuppressive agents. Clinically the disease most commonly presents with abrupt onset of fever, chills, malaise, and prostration. Physical findings in the chest are usually unimpressive, but may reveal fine scattered rales. Hepatosplenomegaly is infrequent in the adult patient. Repeated funduscopic examination may be rewarding, for choroidal tubercles have been reported in as many as 60 per cent of patients in reported series.⁹ Meningeal involvement is to be suspected in all cases, and evaluation should include lumbar puncture. Laboratory evaluation should also include smear and culture of sputum, urine, and pleural fluid when present, as well as culture and histology of pleural tissue. Liver and bone marrow biopsy are very useful; it is essential that all biopsy specimens be submitted for both histologic and cultural study.

Various hematologic changes have been reported as common findings in miliary tuberculosis: anemia, leukopenia, thrombocytopenia, pan-

cytopenia, leukocytosis, leukemoid reactions, and monocytosis.^{3, 11} Recognition of miliary tuberculosis by roentgenography may be difficult, particularly in the early stages. We have been impressed by the number of patients with classical miliary lesions of the lung who presented with normal chest x-rays when initially seen, and then rapidly developed x-ray findings. Serial chest films in the course of a fever of unknown origin are essential. The tuberculin reactions, particularly in the elderly, may be weakly positive or even negative. Tuberculin negativity in this setting is often due to diminished immunologic response of the patient, but errors in technique, interpretation, or faulty antigenic material occur. So-called "areactive" or "nonreactive" tuberculosis deserves mention.^{10, 11} This is a rare, acute, and usually malignant form of disseminated tuberculosis which has been described in adult patients who usually have pre-existing hematologic disease such as leukemia, or lymphoma. Clinically it appears as an overwhelming infection, and pathologically it is characterized by failure to develop granulomatous tissue and/or cellular response.

Diagnosis usually depends upon biopsy of lymph nodes, liver, or bone marrow. Since the histologic findings are often nonspecific it is urgent that cultures be inoculated from the biopsy specimen. While sputum may contain tubercle bacilli, it is common experience that this evidence is lacking in early phases of illness. As the lesions progress they may eventually break down and communicate with a bronchus, yielding organisms in the sputum. In the early stages the lesions, having been distributed via the blood stream, have no such communication.

Tuberculous Meningitis

Meningitis continues to be a dreaded complication of tuberculosis. It may occur as a result of hematogenous dissemination in primary tuberculosis, or it may be due to the reactivation and extension of an old focus from within the brain into the subarachnoid space, or from an adjacent area of tuberculous osteomyelitis of the spine. In the past tuberculous meningitis was seen principally in young children; today it is seen more commonly in adults and must be differentiated from other causes of meningitis.

In our experience at the Harlem Hospital Center, where we have encountered 36 cases of tuberculous meningitis over the past 6 year period, early recognition of the disease has proven difficult. Indeed, although the classical symptoms of meningitis were present in most patients, the condition was often initially misdiagnosed as delirium tremens, cerebrovascular accident, head injury with concussion, heroin withdrawal syndrome, seizure disorder, and metabolic coma. Several patients presented with a variety of nonspecific neurologic signs which could be of diagnostic significance only when tuberculosis was considered in the differential diagnosis.

The classical descriptions of tuberculous meningitis are well known and emphasize the insidious and protracted onset, the generalized systemic symptoms, the subtle or overt changes in personality, cranial nerve palsies, nuchal rigidity, and gradual progression to stupor and coma. On the other hand, the onset may be abrupt, the patient manifesting severe headache, stiffness of the neck, stupor, or delirium. In practically all

cases increasing rigidity of the neck is associated with Brudzinski's sign. The fever of tuberculous meningitis is not very constant or typical; it is usually irregular and generally does not rise above 103 to 104° F.

The cerebrospinal fluid changes characteristically consist of: elevated pressure, clear or opalescent fluid with, on occasion, the formation of a protein pellicle on standing, increased protein concentration in the fluid, decreased sugar concentration, and pleocytosis. Acid-fast organisms are not frequently seen on smear and staining of the cerebrospinal fluid, whereas culture of the fluid is more rewarding. Initially the cell count may vary from a few cells upward to 400 cells with a high percentage of polymorphonuclears. Marked elevation in cell count up to 3000 and 4000 may be encountered during the disease and may reflect an acute hypersensitivity reaction.¹⁵ The cerebrospinal fluid sugar may be normal at an early stage of the disease, and may be normal even at an advanced stage. Recently we examined a patient whose first three cerebrospinal fluid examinations showed no cellular response, although the cultures of those same specimens were eventually positive on culture. The protein content is classically elevated, but it may be within normal range at times. The early cerebrospinal fluid findings may be confused with those of aseptic meningitis, viral encephalitis, partially treated bacterial meningitis, brain abscess, sarcoid, or fungal meningitis, or carcinomatosis of the leptomeninges.

Serial examinations of the cerebrospinal fluid are of importance in following the evolution of the disease and the efficacy of drug therapy. Moreover, it may occasionally be necessary to perform carotid arteriogram during the course of the disease to determine ventricular size, followed by ventriculography and a shunting procedure where indicated as a life-saving measure.

Important clues to diagnosis are a history of tuberculous contact, a positive tuberculin, and roentgenographic evidence of pulmonary tuberculosis; but these factors are also variable, since frequently no history of contact is elicited, the tuberculin reaction may be suppressed temporarily, and the chest film may show no evidence of either previous or current disease.

Tuberculous Pericarditis

In the United States the incidence of tuberculous pericarditis is reported to account for from 7 to 10 per cent of all pericarditides; another 10 per cent of pericarditides are suspected to be tuberculous in origin but are classified among idiopathic or acute benign pericarditis for lack of bacterial confirmation. The difficulty in establishing a definite tuberculous etiology either by way of bacteriologic or histologic means is well known. Clinical recognition of the disease is dependent upon a high index of suspicion, and is of primary importance if the condition is to be managed appropriately.

The onset of acute tuberculous pericarditis is frequently abrupt and occurs concomitantly with the onset of fever; the latter is generally high and swinging. This mode of onset occurs in about 20 per cent of cases; an insidious course over a period of weeks or months is more usual. Dyspnea on exertion or even at rest is characteristic and early in appearance.

Chest pain may be a prominent symptom when present but occurs in a minority of cases; it is more characteristic of acute benign or viral pericarditis. When pain is present it is often "sticking," located over the precordium when the heart is in closest contact with the chest wall, and may be exacerbated by cough, respiration, swallowing, or position. When the pain is dull and aching in nature, it may be confused with that of myocardial infarction.

Pericardial friction rub is frequently elicited in the acute stage; pericardial effusion and occasionally pleuropericardial effusion, and cardiac tamponade all may occur as acute manifestations. The chest x-ray in the latter instance is suggestive; but in the acute stage may reveal a normal cardiac silhouette. The electrocardiogram may be confirmatory; atrial arrhythmias are not unusual.

The only definite means of establishing diagnosis is isolation of *M. tuberculosis* from culture of the effusion of pericardial tissue (biopsy). In a survey of 214 patients with a clinical diagnosis of tuberculous pericarditis, positive diagnosis was established by bacteriologic methods in only 15 per cent and by histologic examination in 4.6 per cent.⁴ The difficulty of bacteriologic and histologic diagnosis in the acute stage has been previously noted. The white blood count is usually within normal range. The tuberculin skin test is positive in the vast majority of patients. At Harlem Hospital roentgenographic evaluation consists of a two-fold diagnostic approach: echocardiography to determine the presence of effusion, intravenous carbon dioxide contrast study to determine the presence of pericardial thickening. If pericardiocentesis is indicated, it is performed by the cardiologists, employing the subxyphoid approach under electrocardiographic monitoring (precordial lead attached to the aspirating needle) to avoid myocardial trauma. In many cases it is advisable to have surgical stripping performed, serving both diagnostic and therapeutic goals. The approach by needle is not without danger and should be attempted only by experienced persons. When pericarditis occurs in elderly patients who have other cardiac problems, the prognosis is guarded; in other patients the results of treatment are usually good. It is generally agreed that corticosteroids, in conjunction with specific anti-tuberculosis agents, are of value in the treatment of tuberculous pericardial effusions, especially when the latter are massive or recurrent.¹²

Tuberculous Peritonitis

Tuberculous involvement of the peritoneum is infrequently encountered nowadays, although its occurrence in endemic areas is still quite high. In these areas bovine tuberculosis remains an important etiologic factor. Tuberculous peritonitis result from rupture of a caseous lymph node, enteritis caused by the ingestion of bacilli originating in active pulmonary lesions, or spread from active pelvic tuberculosis in the female. Tuberculous salpingitis is associated with sterility and ectopic pregnancy, risks that should be anticipated in this condition.

At the Harlem Hospital, we continue to encounter one or two cases of tuberculous peritonitis each year. Although the symptoms of tuberculous peritonitis tend to be insidious in onset, the disease may be acute, with rapid appearance of abdominal pain and swelling associated with chills,

fever, and peripheral leukocytosis. When acute, the disease may resemble pyogenic peritonitis. Ascitic fluid may be a prominent finding; Burak and Hollister at the Boston City Hospital pointed out the difficulty in recognizing tuberculous peritonitis when there is coexistent alcoholic cirrhosis and ascites.² In their experience the ascitic fluid in such cases was often physically, chemically, and bacteriologically identical. Usually examination of the fluid reveals a mononuclear pleocytosis and elevated protein concentration. This difficulty in finding acid-fast organisms on smear of ascitic fluid is well known; culture of peritoneal fluid and tissue has a slightly higher yield. Presumptive diagnosis is generally made on the basis of histopathologic findings on tissue obtained either at peritoneoscopy or at laparotomy.

TREATMENT

Principles of treatment are well established and can be found elsewhere. A brief summary follows, with comments on aspects of treatment of tuberculosis under special circumstances.

1. Multiple drugs should be administered in all cases of "acute" disease, three drugs in most cases; this is particularly applicable to tuberculous pneumonia, where the presence of large numbers of organisms predisposes to the emergency of resistant forms.

2. Any regimen for acute tuberculosis should include isoniazid or rifampin, and possibly both. (This combination is still under study but appears very promising.)

3. Supportive therapy is vital, for dehydration, electrolyte imbalance, malnutrition, and other medical diseases all influence the precarious balance between survival and death.

4. Drugs must be carefully monitored for possible toxicity.

5. Drugs should be administered without interruption, and therapy altered only if toxicity or bacterial resistance occurs.

6. The use of corticosteroids is controversial, except for their use in associated adrenal insufficiency. Controlled studies of corticosteroid therapy were carried out and the following conclusions arrived at:^{5, 7}

- (a) Corticosteroid administration for a limited period, in conjunction with effective chemotherapy, may reverse the toxic manifestations of hyperacute tuberculous pneumonia, and promote subjective improvement in the desperately ill patient.

- (b) Corticosteroids appear to accelerate the clearing of exudative infiltrates without speeding sputum conversion or cavity closure.

- (c) Corticosteroids appear to have value in controlling the effusions of tuberculous pericarditis and pleurisy and, hopefully, in preventing adhesive scarring; they can be of significant help in reversing cerebral edema in meningitis.

- (d) The anticipated benefits of corticosteroid treatment are associated with hazards. Patients with acute tuberculosis are severely debilitated. At least 50 per cent will have other medical-surgical problems. Some of these problems may be exacerbated by the administration of steroids.

(e) It is important to remember that systemic steroids are capable of repressing or suppressing tuberculin reactivity,¹³ and that skin testing should be carried out before initiating steroid therapy.

CONCLUSION

Hospital admissions for tuberculosis are decreasing. Physicians lacking experience with this disease, especially its acute forms, may not consider the diagnosis. This oversight may be fatal, as a favorable response to treatment is best achieved by early chemotherapy. For best therapeutic results, the diagnosis must be considered, the patient rapidly evaluated, and therapy initiated in highly suspicious cases while bacteriologic confirmation is pending.

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Gram-Negative Bacteremic Shock

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Gram-negative bacteremia, found with increasing frequency in adult hospital services, constitutes a major problem. Most studies indicate that 70 to 90 per cent of patients who develop blood stream infections are already hospitalized when infection occurs, and that there is a high incidence of shock and a high fatality rate associated with these infections.

The meaning of the term "shock" is controversial, knowledge of the pathophysiology of the shock syndrome is incomplete, and there is no single etiologic or functional definition. Perhaps it is best to consider shock as a syndrome consisting of responses to inadequate tissue perfusion and cellular hypoxia.

PATHOPHYSIOLOGY

The toxic effects of endotoxin on the polymorphonuclear leukocyte are now well established, and it seems possible that direct effects on other cells account for some of the phenomena of shock. Endotoxin, found only in the bacterial cell wall, is a complex lipopolysaccharide bonded to cell wall protein. When released by death of bacteria, it activates the complement system, and vasoactive substances (histamine, serotonin, epinephrine, norepinephrine, and kinins) are liberated from platelets and white cells. Stagnant anoxia in the microcirculation follows, primarily in the viscerocutaneous organs (including the lungs), reducing effective circulating blood volume. Fluid loss from the vascular space further reduces the effective circulating volume as elevated hydrostatic pressure within congested capillaries forces plasma into tissues, and as capillary membrane changes occur independently of hydrostatic or colloid osmotic pressure (Fig. 1). Because of the potency of endotoxin, deterioration of the microcirculation, which takes hours to occur in hemorrhagic shock, can occur in minutes or seconds following endotoxic shock.

To understand current concepts of the pathophysiology of shock and its management two factors have to be understood—cellular hypoxia, and the microcirculation.

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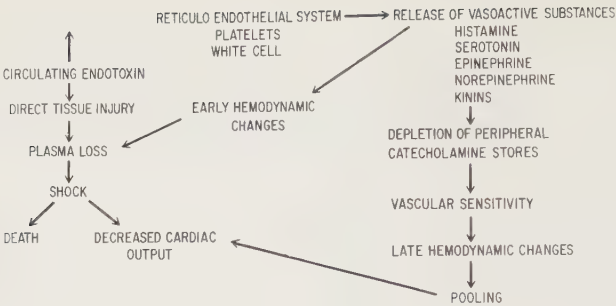


Figure 1. Effect of circulating endotoxin.

Cellular Hypoxia

Figure 2 briefly diagrams the cellular metabolism of glucose. Each six-carbon glucose molecule is converted into two three-carbon pyruvate molecules with the release of two hydrogen ions and energy in the form of ATP. The hydrogen ions combine with oxygen to form water. If oxygen is not available, each hydrogen ion combines with a pyruvate molecule to form lactate, which then accumulates as a metabolic waste. At each subsequent step energy is released, and oxygen combines with hydrogen ions to form water, or with carbon ions to form carbon dioxide. The water and carbon dioxide are excreted; the energy is stored as phosphate bonds in ATP. If oxygen uptake by the cells is diminished, glucose metabolism slows, with a decrease in ATP and an increase in hydrogen ions. In shock, blood lactate increases, metabolic acidosis occurs, and tissue stores of ATP decrease. With lack of energy from ATP, the sodium-potassium pump fails and intracellular potassium is released into the extracellular and intravascular spaces. With further depletion of cellular energy stores protein synthesis stops, lysosomes break down and release their enzymes (proteases, esterases, phosphatase), and autodigestion and destruction of the cell follow. At this point the machinery is wrecked.

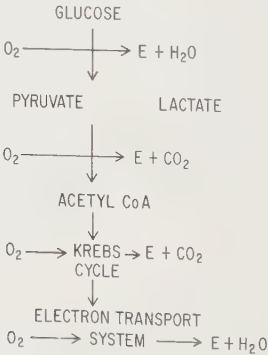


Figure 2. Cellular metabolism of glucose.

Microcirculation

Microcirculation (Fig. 3) refers to an individual arteriole and venule with interposed capillary bed. Blood flow through the capillary bed is regulated by the mean pressure gradient and the total resistance between the arteriole and venule. The mean a-v gradient may vary between 40 and 100 mm. Hg—a 250 per cent change. Resistance is altered by changes in three factors: critical closing pressure (capillary intraluminal pressure minus tissue pressure), viscosity of blood, and vascular tone.

Vascular tone, the most important factor regulating flow in the microcirculation, is influenced by the following mechanisms:

(1) Neurogenic. Somatic afferent (sensory) fibers respond reflexively to pain or irritation by dilating the underlying capillary bed. Autonomic vasoconstrictor fibers from the thoracolumbar ganglia, which supply most arterioles (except those in the heart or brain), produce vasoconstriction by release of norepinephrine at the myoneural junction. Lack of vasoconstrictor fibers in heart and brain arterioles explains the disproportionate maintenance of blood flow to these two organs when the rest of the vascular tree is constricted in shock. There are also autonomic vasodilator fibers which run with vasoconstrictors, but have a different central-connection. These fibers supply the viscera and produce active vasodilatation.

(2) Humoral control of the microcirculation—primarily the function of the catecholamines, epinephrine and norepinephrine. Epinephrine acts on both arterioles and precapillary sphincters to decrease skin blood flow and increase muscle blood flow. The catecholamines act on receptors on the circular smooth muscles in the vessel wall—alpha receptors producing vasoconstriction; beta receptors, vasodilatation. Thus, the different response of vessels in skin and muscle is due to the difference in distribution of alpha and beta receptors. Norepinephrine acts only on the alpha receptors, therefore producing only vasoconstriction. Other humoral agents—histamine, bradykinin, kallidin and oxytocin—are vasodilators which counteract the vasoconstrictive effects of catecholamines.

(3) Local regulation. The smooth muscle in arterioles and precapillary sphincters has an autogenous tone: isolated arterioles remain partially contracted. Physical factors such as cold, trauma, and intraluminal pressure may increase the autogenous tone. Increased metabolic activity of the adjacent tissue will decrease the smooth muscle vascular tone independent of neural and humoral influence—perhaps in response to changes in P_{O_2} , P_{CO_2} or pH.

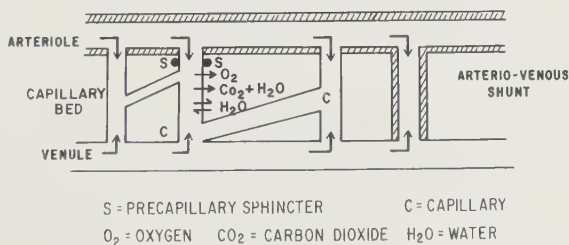


Figure 3. Microcirculation.

The functions of the microcirculation are gas, solute, and fluid exchange. The efficiency of these functions is regulated by the total surface area of capillaries being perfused and the time blood is in contact with the capillary wall. When blood flow through an arteriole increases, and precapillary sphincters relax, a greater proportion of the capillary bed is perfused, and efficiency of capillary function increases. If the arteriole and precapillary sphincters contract, the function of the capillary bed decreases.

Every organ participates in the shock syndrome by altering its function as a defense against the metabolic insult.

Recently attention has been directed to pulmonary problems in shock, because pulmonary insufficiency and lung lesions are frequently associated with shock. The lung may be a critical target organ. This syndrome of progressive pulmonary insufficiency, a lethal complication after shock, has been emphasized as a major cause of death in those who survive more than 24 hours after the shock syndrome.

There is an early period of hyperventilation with alkalosis, followed by a transient period of deceptively good pulmonary function, then progressive desaturation requiring intubation and tracheostomy. Then pneumonia follows, with shunting of blood. The terminal event is pulmonary edema with hypoxia and acidosis, culminating in asystolic cardiac arrest. It is now thought that the lung lesion may develop as a primary manifestation in shock, that is, as an intrinsic response to tissue injury. Histologically there is vasculitis, enlargement of alveolar lung membrane, widening of septa, and hyaline membrane formation.

When those organs—heart, lungs, kidney, adrenal, pancreas, gastrointestinal tract, reticuloendothelial and hematologic system—that normally compensate for the metabolic disturbance suffer from overall reduction of blood flow, normally expected corrective effects are not forthcoming, and death may result.

ORGANISMS

Table 1 gives a classification of the gram-negative organisms. The commonest organisms responsible for bacteremia belong to the family Enterobacteriaceae, which accounts for about 35 per cent of the infections. *E. coli* remains the most common causative organism in the family. Bacteremia due to *Klebsiella*-*Enterobacter*-*Serratia* group is second in incidence to *Escherichia*, accounting for about 20 per cent of cases. Of this group, *Klebsiella* causes about 80 per cent of clinical infection; *Enterobacter*, about 15 per cent; *Serratia* the remainder. Bacteremia due to *Proteaeae* is third in incidence, accounting for about 15 per cent of cases, but is often lethal. Bacteremia caused by *Proteus* organisms is far more common than that caused by *Providencia* organisms. Of the *Proteus* group, *P. mirabilis* causes 70 to 80 per cent of clinical infection; *P. vulgaris*, *P. morganii* and *P. rettgeri* cause the remainder. Bacteremia due to *Edwardsiella* is rare, probably accounting for less than 10 per cent of cases due to Enterobacteriaceae.

Table 1. *Classification of Gram-Negative Organisms*

<i>Enterobacteriaceae</i>	<i>Other</i>
Escherichieae	Pseudomonas
Escherichia coli	
Shigella	Mimeae
Salmonelleae	Herellea vaginicola
Salmonella	Mima polymorpha
Arizona	
Citrobacter	Alcalagenes
Klebsielleae	
Klebsiella	Flavobacterium
Enterobacter (formerly Aerobacter)	
E. cloacae	Moraxella
E. aerogenes	
E. liquifaciens	Bacteroides
E. hafnia	
Serratia	
Proteeae	
Proteus	
P. mirabilis	
P. vulgaris	
P. morganii	
P. rettgeri	
Providence	
P. alcalifaciens	
P. stuartii	
Edwardsielleae	
Edwardsiella tarda	

In recent years bacteremia due to *Pseudomonas* has attained an overall incidence higher than that due to *Proteus* in some institutions. The other pathogens listed are not common causes of bacteremia. Failure to obtain anaerobic cultures may conceal the fact that bacteremia due to *Bacteroides* may be present. Although these organisms account for only a small percentage of reported cases of bacteremia they are significant because prolonged morbidity and a high death rate are associated with *Bacteroides* bacteremia.

SOURCE OF INFECTION

The portal of entry for gram-negative organisms is the urinary tract in 50 to 60 per cent of patients, and the gastrointestinal tract in 25 per cent (biliary tract, 10 per cent; other areas of the gastrointestinal tract, 15 per cent). The female genital tract is the source in 5 per cent, usually in postabortal and postpartum women. In 5 per cent the skin and postoperative wounds are responsible. In 10 to 15 per cent the source is unknown. The respiratory tract, though not a common portal for gram-negative bacteremia, may give rise to *Bacteroides* infection. *Pseudomonas* bacteremia also has a respiratory portal, usually in patients using contaminated aerosoles; though skin (in burned patients) and urinary tract are more common for *Pseudomonas* infection.

PREDISPOSING FACTORS

Seventy per cent of gram-negative infections are acquired in the hospital. The incidence is highest in the aged and in neonates. Susceptibility is increased in postpartum women and after septic abortion.

The incidence of gram-negative sepsis is increased after urologic procedures or gastrointestinal operations. About 10 per cent of patients have malignant neoplasms; those being treated with radiomimetic drugs are especially susceptible. Ten per cent of patients have diabetes mellitus, in which the portal is almost always the urinary tract. Five per cent have severe hepatic disease.

Fifteen per cent of patients have hematologic disease. The diminished resistance to infection in these patients may reflect: (1) defect in gamma globulin, as in chronic lymphatic leukemia, lymphoma, and multiple myeloma; (2) inadequate neutrophilic response, as in acute leukemia, chronic granulocyte leukemia, agranulocytosis, or aplasia; (3) iatrogenic factors, including treatment with adrenal steroids, anti-metabolites, and antibiotics. In hematologic diseases bacteremia is not uncommonly due to *Pseudomonas*.

CLINICAL FEATURES

The early stages are characterized by "infectious" symptoms. The patient is alert, has warm flushed skin, full-bounding pulses, moderate hypotension, moderate urinary output, and progressive pyrexia. About 98 per cent of patients have fever, ranging from 101 to 106° F (oral), which may be intermittent, remittent, continuous, or variable. The onset of bacteremia is manifested by fever and chills in about 60 per cent of patients, by spiking fever without chills in approximately 25 per cent, and by a gradual onset of malaise and fever in about 15 per cent. Twenty to 30 per cent of patients manifest their infection by sudden circulatory collapse or bacteremic shock. Headache is common. All patients have some degree of prostration, but delirium and stupor are rare. Vague myalgia, restlessness, apprehension, and agitation are initial manifestations in a few patients. Coma is rare and usually reflects an underlying condition such as hepatic failure, uremia, or diabetic acidosis. Anorexia is usual, but vomiting, abdominal distention, and diarrhea often reflect an underlying disease (chronic ulcerative colitis, uremic enterocolitis, or pelvic abscess).

Diarrhea can occur in bacteremia without underlying intestinal disease; classically this suggests *Bacteroides* or *Salmonella* infection, although it may be associated with infection by other gram-negative bacilli. Diarrhea occurring after bacteremia is established suggests staphylococcal enterocolitis complicating antibiotic therapy.

If appropriate therapy is instituted in this early stage the prognosis is good.

Human bacteremic shock is not the result of a single hemodynamic alteration: some patients have reduced cardiac output and normal or

increased peripheral arterial resistance; others have essentially normal cardiac output and reduced peripheral resistance. As inadequate perfusion of vital tissues and organs with oxygenated blood proceeds, signs of shock develop. These signs occur in 10 to 40 per cent of adults who develop gram-negative bacteremia. The first clue to the presence of shock is often provided by an alteration in the patient's mental status, with confusion and disorientation predominating. As the severity of the hypotension increases the patient becomes semicomatose and has pale, damp, cold skin, collapsed superficial veins, and feeble pulses. The distal extremities, and later the ear lobes and tip of the nose, become cyanotic. Tachycardia is common, but in the elderly a relatively slow beat may be noted. Respiratory distress with shallow hyperpnea but without signs of pulmonary congestion may be apparent. In patients having advanced bacteremic shock, urine flow is often reduced to 20 ml. or less per hour. When patients are seen in this late stage the prognosis is poor.

Recently blood concentrations of lactate and pyruvate have been studied as possible indices of impending shock and its reversibility. Metabolic acidosis, which is common in bacteremic shock, may be due largely to an increase in lactate ions. As a preliminary impression the severity of shock appears to parallel the concentration of blood lactate: a high level of blood lactate (or lactic acidosis) early in shock appears to indicate a poor prognosis, while an initial value of less than 10 mEq. per liter, which drops rapidly with treatment, may indicate a better prognosis. Significant lactic acidosis which occurs when the ratio of lactate to pyruvate is greater than 10:1 results from reduced blood flow, tissue hypoxia, and increased anaerobic metabolism.

Laboratory findings in gram-negative bacteremia include elevation of blood urea nitrogen, hyperkalemia, and decreased values for serum sodium, chloride, and bicarbonate. Leukocytosis is usually present, but a normal number of leukocytes is not rare. In an occasional case leukopenia, replaced shortly by leukocytosis, is the initial manifestation of complicating shock. In *Pseudomonas* bacteremia marked and persistent leukopenia occurs. Patients with underlying hematologic disease are peculiarly predisposed to *Pseudomonas* bacteremia.

Notable clinical features sometimes suggest that *Pseudomonas* is the pathogen. First are skin lesions, most often seen in the anogenital area and the axilla, known as "ecthyma gangrenosum." The lesion begins as macule or a vesicle, becomes pustular, and sometimes sloughs to form a necrotic ulcer. Biopsy of the lesion may reveal bacilli in the walls of blood vessels; cultures may show *Pseudomonas* organisms. Petechiae and, rarely, bluish-green discoloration of nail beds also suggest *Pseudomonas* bacteremia. Though jaundice may be noted in bacteremia caused by other gram-negative bacilli, its incidence is increased in *Pseudomonas* bacteremia.

Diarrhea beginning before antibiotic therapy, and ending with recovery, occurs in about one third of cases of *Bacteroides* bacteremia. Also in about one third, foul-smelling exudates are noted; only rarely do these have the stale butter-like or cheesy odor characteristic of *Bacteroides* infection.

CLINICAL, HEMODYNAMIC, AND CHEMICAL MEASUREMENTS

Clinical, hemodynamic, and chemical measurements should be obtained frequently in the patient in shock. Such records will help to define severity of illness and measure efficacy of therapy. The following variables should be recorded at frequent intervals:

States of consciousness	- restless, anxious, agitated, depressed
Skin	- temperature, moistness, color, turgor
Mucous membranes	- color, moistness
Nail bed	- color, capillary refill
Peripheral veins	- collapsed or distended
Pulse	- rate, quality
Respirations	- rate and depth
Urinary output	- hourly volumes

Management of shock is usually based on frequent measurements of central venous pressure, blood pressure, and pulse rate. Graphic recordings of these values every 15 minutes (more often if needed) gives a general picture of changes and trends in the patient's condition, and reflects the response to treatment. In general, the shock patient has a narrow pulse pressure and tachycardia. Widening of pulse pressure and fall in pulse rate are signs of hemodynamic improvement. Progress toward recovery or deterioration is best signalled hemodynamically by considering together the response of central venous pressure, arterial pressure, and urinary output.

Shock has sometimes been considered a problem in the arterial blood pressure, for this is an easily measured parameter. In fact, a more fundamental problem appears to be cellular damage from inadequate capillary blood flow (though this is more difficult to measure), while hypotension may be a relatively late phenomenon. In severe shock vasopressors may raise the blood pressure to normal or hypertensive levels while tissue blood flow is progressively reduced. Thus, measurement of arterial blood pressure or cardiac output does not define the adequacy of tissue perfusion, and arterial blood pressure alone is a poor indicator of the severity of shock.

PREVENTION

Shock becomes irreversible when persistent tissue anoxia produces tissue damage. The best treatment is prophylaxis. Much can be done to prevent bacteremia and shock by preventing inoculation of organisms in the hospital environment. It is essential that proper selection, care, and aseptic technique be employed in using Foley and intravenous catheters and respirator equipment. Using a closed bag urinary drainage system and 3-way Foley catheters with constant irrigation dramatically reduces the incidence of bacterial inoculation in patients who require urinary catheterization. The use of condom catheters rather than Foley catheters has also decreased the incidence, which is about 10 per cent when a

catheter is passed in and out of the bladder. Large bore intravenous catheters carry a higher incidence than 19 gauge scalp vein needles. After 48 hours the incidence of infection rises; therefore intravenous catheters must be changed every 48 hours, with Bacitracin ointment used at the point of entry with every change. Cutdowns have a higher incidence. Tracheostomy tubes and liquids used should not be left open.

MANAGEMENT

The problems we face in gram-negative shock are threefold: bacteremia, endotoxin release causing vascular collapse, and shock itself. Each requires specific therapy. Generally, treatment should aim at alleviating the cause, correcting various metabolic and hemodynamic changes, and restoring tissue perfusion. Therapy must be started early and pursued vigorously – with attention focused on support of the vulnerable heart, lungs, and kidneys.

FLUID REPLACEMENT. Above all, the atrial filling pressure must be maintained at a level adequate to produce an effective cardiac output. An initial trial of fluid loading is now accepted as a rational first approach to patients in shock with normal or reduced central venous pressure (CVP). Baseline CVP and urinary output are obtained for 15 to 30 minutes. Five per cent dextrose in water is then infused at a rate of 20 ml. per min. for 10 to 15 min. CVP is measured every 3 minutes during infusion and the patient is carefully watched for evidence of pulmonary edema. If CVP rises more than 3 cm. the infusion is stopped and CVP observed. If CVP returns to previous level in next 3 minutes the infusion is re-started. When there is a favorable response in arterial blood pressure without significant rise in venous pressure a state of hypovolemia is present. A rapid rise in venous pressure indicates that the heart is loaded to capacity. All other methods can be expected to fail if adequate fluids are not administered.

ACIDOSIS. Preventing lactic acidosis is exceptionally important. Most patients seen early tend to have hyperventilation and respiratory alkalosis. Such patients have a much better chance of survival if they do not go into acidosis, while those first seen in acidosis have a mortality rate approaching 100 per cent. Almost all patients develop some degree of lactic acidemia, which worsens if the patient is poorly ventilated. Bicarbonate is usually not necessary if the right things are done first; but if acidosis does become a problem, and correcting the CO_2 does not help, it may be useful to give sodium bicarbonate, the standby of buffer therapy. In severe metabolic acidosis the amount of bicarbonate needed to buffer the extracellular space may be roughly determined using the following formula:

$$\begin{aligned} \text{Dosage (mEq.)} &= 0.2 \times \text{body weight (kg.)} \\ &\times (27 \text{ mEq./L.} - \text{sodium bicarbonate mEq./L.}) \end{aligned}$$

In mild acidosis, half the calculated dose is given.

ANTIBIOTICS. Since bacteremia is the obvious underlying cause of shock, prompt treatment of infection is indicated: treatment with an anti-

biotic to which the organism is susceptible results in significant reduction in mortality. Cultures of blood, urine, and any exudate should be obtained quickly, and antibiotic therapy started. In vitro inhibition tests are mainly of retrospective value in the management of bacteremia, because therapy must often be started empirically before such data is available. Waiting until results of tests are available would mean a delay of 24 to 48 hours, increasing the chance of death. Awareness of a primary nidus of infection, underlying disease, or predisposing therapy may suggest the causative organism. If on subsequent receipt of inhibition tests the bacilli are resistant to the drug being given, or if the patient is not progressing well, the empirical regimen is changed. When progress is unsatisfactory after 12 to 24 hours, and inhibition tests remain unreported, the regimen may be changed empirically.

Table 2 gives the sensitivity of gram-negative organisms to antibiotics. To date there is no single agent that assures "coverage" against all such organisms. At present, gentamycin, which has a wide spectrum against gram-negative bacteria, is the best first line drug for use before return of cultures. Carbenicillin is excellent for *Pseudomonas*. Many combinations of antibiotics are available—Keflin and kanamycin; gentamycin and carbenicillin; colistin and Keflin or polymyxin B; ampicillin and kanamycin, colistin, or polymyxin B. When using combinations of antibiotics it is best to avoid two toxic drugs. All antibiotics should preferably be given intravenously; later, intramuscular injections can be used.

STEROIDS. Controversy regarding efficacy of corticosteroids in endotoxic shock arose partly because of differences in dosage used. If steroids are used at all they should be given in doses equivalent to 2 to 6 gm. hydrocortisone per 24 hours for 48 to 72 hours, after which they can be discontinued abruptly without evidence of adrenal insufficiency or untoward effects. An initial dose of 1 gm. hydrocortisone or its equivalent should be given initially and repeated every 4 to 6 hours. The drug administered as a single bolus is more effective than when given as an intravenous drip. There is no contraindication to using steroids in septic shock even in patients with peptic ulcer disease, diabetes, or other conditions which ordinarily would preclude the use of steroids. In bacteremia without shock, or with "warm shock," they may not offer any advantage. It has been shown that massive doses of steroids help to increase the survival rate by a significant degree in septic shock. The beneficial effects have been attributed to stabilization of lysosomal membranes, and to a tendency for massive doses of steroids to normalize cardiac output and total peripheral resistance.

CARDIOVASCULAR SUPPORT. Septic shock is a confusing entity with a complex picture and several hemodynamic patterns. Support with vasoconstrictor, isotropic, or vasodilator drugs must be based on hemodynamic measurements. The group with low cardiac output may respond to drugs such as isoproterenol or phenoxybenzamine. Conversely, use of these drugs in the high cardiac output state is contraindicated. Fluid repletion should precede their use. Isoproterenol (Isuprel), in amounts of 3 to 15 micrograms per minute in 5 per cent glucose in water reduces peripheral resistance and increases arterial pressure and cardiac index.

Table 2. Antibiotics to Indicated Organisms

	GENTAMYCIN	AMPICILLIN	KANAMYCIN	POLYMYXIN B	TETRACYCLINE	CEPHALOTHIN	COLISTIN
Dosage per 24 hours in divided doses intravenous	175-350 mg.	4-12 gm.	1 gm.	150-200 mg.	1-2 gm.	2-6 gm.	100-300 mg.
Intramuscular dose per 24 hours	175-350 mg.	4-6 gm.	1-1.5 gm.	150-200 mg.	50%	4-6 gm.	100-300 mg.
<i>E. coli</i>	+	+	+	+			
<i>Salmonellas</i>							
<i>Salmonella</i> and <i>Arizona</i> (<i>Citrobacter</i>)		+	+	+	+		
<i>Enterobacter</i>	+		+	+	+		
<i>Klebsiella</i>	+	30%	+	+	30%	+	
<i>Serratia</i>	+		+				
<i>Proteus</i> (indole-negative, 80-90% of cases)	+	+	+			+	
<i>Proteus</i> (indole-positive, 10-20% of cases)	+		+		+	+	
<i>Edwardsiella</i>							
<i>Pseudomonas</i>	+	+	+	+	+		
<i>Mimeae</i>			+	+	+		
<i>Bacteroides</i>					+	+	

Toxicity: Nephrotoxic: streptomycin, kanamycin, polymyxin B, colistin, cephalothin
Ototoxic: gentamycin (vestibular), streptomycin, kanamycin (auditory)
Cerebellar ataxia: polymyxin B, colistin
Respiratory depression (due to curareform effects): streptomycin, kanamycin, polymyxin B, colistin
Hematotoxic: chloramphenicol

There is no unequivocal evidence that either alpha or beta drugs favorably influence the outcome of septic shock. The initial enthusiasm for drugs such as levarterenol (Levophed) and metaraminol (Aramine) has been tempered by better understanding of the mechanism of shock. Rational treatment is to improve blood flow to vital organs and secondarily restore effective blood pressure, since increased blood pressure is not necessarily accompanied by increased blood flow.

Phenoxybenzamine (Dibenzyline) reduces total peripheral resistance and central venous pressure, and only modestly increases cardiac output. If norepinephrine is added to the regimen the cardiac output could be augmented. Several clinical reports have recently suggested that dopamine, an intermediate in the synthesis of norepinephrine and epinephrine, may be effective in increasing myocardial contractility without excessive peripheral vasoconstriction and that in endotoxic shock it may be effective in reducing splanchnic pooling.

There is no satisfactory way to choose a vasoactive drug. A therapeutic trial based on gross observation of circulation to the skin and periphery seems a reasonable clinical approach at present.

VENTILATORY SUPPORT. The most frequent single cause of death in shock is failure to achieve adequate ventilation. The oxygen tension (arterial P_{O_2}) should be kept more than 70 mm. Hg. Even after recovery from shock patients must be watched closely for sudden respiratory distress and evidence of ventilation insufficiency, which may signal development of "shock-lung" syndrome. If hypoxemia is not corrected by mask and oxygen, it is necessary to intubate the patient.

RENAL SUPPORT. The most common causes of oliguria and renal damage are hypovolemia and hypotension. Adequate hydration with appropriate fluids is therefore imperative. If oliguria persists after re-establishment of cardiac output and blood pressure, fluid restriction is warranted. Mannitol may be used to identify renal damage in shock. If 25 gm. of mannitol given over a 10 to 30 minute period in 100 to 500 ml. 5 per cent dextrose in water does not improve urinary output, it may be assumed that renal damage has occurred, and fluid restriction may be necessary. Further use of mannitol may result in fatal pulmonary edema.

Furosemide, a powerful diuretic, may be given intravenously in doses of 40 mg. to oliguric patients when blood volume and pressure have been restored. If diuresis does not occur within 5 to 10 minutes, renal damage is likely present.

A urine osmolality near that of plasma, urine sodium concentration greater than 60 mEq. per L., and alkaline urine or urine/plasma urea ratio of 10/1 or less strongly suggest renal damage. Rising blood urea nitrogen and serum creatinine, and presence in urine of renal tubular casts, confirm the diagnosis of acute renal damage. Severe hyperkalemia, common in patients with acute renal failure, should be promptly treated.

SURGICAL MANAGEMENT. Surgical incision and drainage of a localized collection of pus is an essential part of treatment. Excising a necrotic gall bladder, a severely infected uterus, or an ischemic bowel segment may be essential for prompt control of the life-threatening bacterial insult.

FAVORABLE RESPONSE. Favorable response to therapy is indicated by improved sensorium and general appearance, decrease in peripheral cyanosis, warming of the skin over the knees, toes, and hands, increased urinary output to at least 40 to 50 ml. per hour, increased pulse pressure, normalization of central venous pressure, and increase in blood pressure.

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The Rapid Differential Diagnosis of Meningitis

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Meningitis is an emergency and early therapy is vital if death or severe disability is to be avoided. The physician must quickly differentiate the various causes of meningeal irritation and initiate appropriate bacteriologic, microscopic, and chemical studies on blood and spinal fluid. Although therapy will have to start prior to obtaining a bacteriologic report, a careful history and physical examination will assist in choosing the most appropriate therapy. Aseptic (viral) meningitis does not require chemotherapy, while bacterial and fungal meningitis do. Pretreatment cultures are vital since incorrect therapy may obscure the diagnosis and delay the start of effective treatment.

HISTORY

Headache, nausea, vomiting, and photophobia are common symptoms of meningitis. In viral meningitis, the patient is usually alert enough to relate these symptoms. In purulent meningitis, the patient is more likely to be stuporous or comatose. Several hours of agitation, personality change, or "waxy flexibility" may precede lapse into a comatose state. The patient is sometimes first sent for psychiatric evaluation, resulting in a crucial delay in diagnosis. Since the development of acute psychoses in previously normal patients may herald the onset of meningitis, such patients deserve medical examination before psychiatric consultation.

PHYSICAL EXAMINATION

Meningeal Signs

Neck stiffness is the most characteristic finding in patients with meningeal irritation. The degree of stiffness is significantly less in viral

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infections when compared to the "board-like" rigidity that usually accompanies bacterial infections, fungal infections, and subarachnoid hemorrhage. The presence of xanthochromia in a centrifuged specimen of cerebrospinal fluid indicates that the bleeding was not the result of a traumatic tap.

Three signs helpful in confirming meningeal irritation in patients whose nuchal rigidity is of uncertain origin are: (1) Brudzinski's sign, in which passive flexion of the neck results in flexion of the knees and hips; (2) Kernig's sign, in which there is pain and difficulty in extension of the knee when the patient lies supine with his thigh perpendicular to his trunk; and (3) the contralateral Brudzinski's sign, in which there is flexion of the patient's opposite hip and knee during the course of being examined for Kernig's sign.¹ Elderly, uncooperative patients who resist flexion of the neck may also resist rotation of the neck. Inflammation of cervical lymph nodes or other tissues in the neck may cause apparent nuchal rigidity. In doubtful cases a lumbar puncture should be performed.

Rashes

Meningococcal rashes are varied and include petechial and morbilliform (measles-like) rashes. Particularly characteristic of meningococcal septicemia are deeply purpuric, irregular triangular lesions occurring most commonly on the lower extremities. The rash may become confluent. Meningococci may be seen on Gram stain from scrapings taken from the border of the rash. Meningococcemia even without meningitis has a high mortality rate and prompt treatment is indicated. Occasionally petechial rashes occur in pneumococcal meningitis if endocarditis is present. Viral infections may also be accompanied by a rash.

Heart Murmurs

The development of a new murmur or a change in a previously observed murmur may indicate the presence of associated bacterial endocarditis. Endocarditis itself may be a complication of the bacteremia of meningitis, or may be the problem initiating meningeal irritation and focal neurologic symptoms by producing septic emboli.⁶ For example, acute staphylococcal endocarditis may produce small septic emboli to the brain, giving rise to transient focal neurologic signs prior to the appearance of a murmur.

SPINAL FLUID EXAMINATION

In cases of suspected meningitis, a spinal tap should be performed on admission. The examiner should note the gross appearance of the fluid and immediately perform a Gram stain, total cell count, and differential count. Obviously, culture of the specimen should be performed routinely. The Gram stain should also be done routinely (Table 1), for occasionally—especially in patients with pneumococcal meningitis—the spinal

Table 1. *Rapid Gram Stain*

1. Place slide under electric light bulb for rapid drying.
2. Heat-fix over flame, specimen side up.
3. Gentian violet—2 seconds.
4. Gram's iodine—2 seconds.
5. H₂O rinse
6. Acetone-alcohol, 1 to 3 seconds (stop promptly when gentian violet is no longer eluted).
7. H₂O rise.
8. 2% Carbol fuchsin or safranin—3 seconds.
9. H₂O rinse.

fluid may show no increase in white cells despite the presence of many bacteria.

Spinal fluid glucose, a simultaneous blood glucose, and spinal fluid protein are also determined on admission. Normally, spinal fluid glucose concentration is approximately 60 per cent of that in blood. Both must be determined concomitantly if the results are to be significant in a patient with hyperglycemia or hypoglycemia. The results of these single tests are often invaluable in assisting in differentiating acute bacterial, chronic bacterial, and viral infections.

Table 2 lists the usual results of spinal fluid examination in the various forms of meningitis.

Table 2. *Usual Findings on Examination of Cerebrospinal Fluid in Different Types of Meningitis*

TYPE OF MENINGITIS	CELLS	GLUCOSE	PROTEIN
Acute bacterial	99% polymorphonuclear leukocytes	Low—characteristically less than 10 mg. per 100 ml.	Increased
Chronic bacterial or fungal	25 to 500 per cu. mm., rarely over 1,000 per cu. mm. Early (days)—polymorphonuclear but less than 95% Later—mononuclear cells predominate	Low—frequently 10 to 25 mg. per 100 ml.	Increased
Aseptic (viral)	25 to 500 per cu. mm., rarely over 1,000 per cu. mm. Early (days)—polymorphonuclear but less than 95% Later—mononuclear cells predominate	Normal	Moderately increased (usually 50 to 100 mg. per 100 ml.)

ETIOLOGY OF MENINGITIS

Bacterial^{2, 7}

On the adult medical service of the Kings County Hospital, the pneumococcus was the commonest cause of bacterial meningitis (Table 3). The pneumococcus is commonly found in children under 1 year of age and in elderly patients, in children with sickle cell disease, in alcoholics (especially with concomitant pneumonia), in patients with meningitis secondary to otitis media, and in patients with recurrent pyogenic meningitis.

The meningococcus is found most commonly in previously healthy adults, with epidemics occurring in conditions of overcrowding and physical stress (such as basic training camps).

Hemophilus influenzae is the commonest cause of bacterial meningitis in children between the ages of 2 months and 5 years. Gram-negative bacilli cause half the cases of meningitis in newborns. They may also cause meningitis in adults: 9 patients with meningitis caused by gram-negative bacilli were diagnosed on the medical service of Kings County Hospital during the same period in which there were 49 cases of pneumococcal meningitis (Table 3). Gram-negative bacillus meningitis is usually secondary to septicemia.

Aseptic (Viral)

The aseptic meningitis syndrome is characterized by acute onset of fever, headache, nausea, vomiting, meningeal signs, and cerebrospinal fluid pleocytosis. Infectious agents other than viruses—e.g., leptospira and trichinella—cause a similar syndrome. In late summer and early fall, various species of Coxsackie and Echo viruses are the likely causes. In late winter and early fall mumps virus is a common cause. Associated clinical manifestations in the patient, or in contacts, may give helpful etiologic clues. These include parotitis, orchitis, or pancreatitis with

Table 3. *Positive Cerebrospinal Fluid Cultures, Department of Medicine, Bacteriology Laboratory, Kings County Hospital, January 1, 1967 to January 31, 1972*

Diplococcus pneumoniae	49
Neisseria meningitidis	16
Alpha hemolytic streptococcus	9
Escherichia coli	6
Anaerobic streptococcus	6
Staphylococcus aureus	5
Beta hemolytic streptococcus	5
Listeria monocytogenes	4
Cryptococcus neoformans	4
Haemophilus influenzae	1
Pseudomonas aeruginosa	1
Vibrio fetus	1
Proteus mirabilis	1
Total	108

mumps infection; pericarditis or pleuritis with Coxsackie B virus; herpangina with Coxsackie A virus; or rash with Echo 9 virus.

Viral studies are not helpful in making a prompt differential diagnosis. The local virus laboratory should be consulted prior to submission of specimens. Because the number of viruses causing aseptic meningitis is large the laboratory will frequently not attempt serologic studies unless a virus has been isolated.

Chronic Bacterial or Fungal

Mycobacterium tuberculosis, *Cryptococcus neoformans*, and *Coccidioides immitis* are the common causes of chronic meningitis. Dissemination of tubercle bacilli through the blood stream occurs during the course of primary tuberculous infection. Years later one or more of the resulting dormant foci may become active. Accordingly, tuberculous meningitis frequently occurs without clinically demonstrable tuberculosis in other organs. The patient is likely to come from a population with a high prevalence of tuberculosis; he may be an inhabitant of an overcrowded urban area, or an alcoholic, or an immigrant from an underdeveloped country.

Cryptococcal meningitis is frequently associated with a serious underlying lymphoproliferative disorder such as Hodgkin's disease or lymphosarcoma. A depressed immunologic response is characteristic of lymphomas. Further depression results from drugs, steroids and anti-metabolites used in the therapy of this family of diseases.

In warm, arid areas of Southwestern United States, especially the San Joaquin Valley of California, *Coccidioides immitis* is the most common cause of chronic meningitis. Coccidioidal meningitis in Caucasians is frequently an isolated manifestation of coccidioidal infection, while in Filipinos, Mexicans, and Japanese, it is usually accompanied by additional disseminated disease.

Other Diseases Causing Cerebrospinal Fluid Pleocytosis

Subarachnoid hemorrhage, meningeal carcinomatosis, leukemia, systemic lupus erythematosus, and sarcoidosis are noninfectious causes of meningeal irritation. Bacterial endocarditis with embolization may also result in white blood cells (usually less than 100 per cu. mm.) and red blood cells in the spinal fluid. If the endocarditis is caused by the pneumococcus or staphylococcus, a secondary meningitis may result; however, with *Streptococcus viridans*, which produces a less fulminant disease, a purulent meningitis is not to be expected. Pyogenic infection in areas contiguous to the meninges may result in cerebrospinal fluid findings of aseptic meningitis. Another disease causing cerebrospinal fluid pleocytosis is amoebic meningoencephalitis. In patients with a recent history of swimming in outdoor fresh water swimming pools, and symptoms suggestive of meningoencephalitis, spinal fluid should be examined for amebae. A wet mount preparation of spinal fluid is helpful in finding these organisms.³

CHEMOTHERAPY OF BACTERIAL MENINGITIS

Treatment will ordinarily be started shortly after the spinal fluid Gram stain is read. By that time, sufficient information will have been collected from history and physical examination to arrive at a preliminary diagnosis. Obviously, patients with rapidly progressing disease should be treated promptly. The physician should personally observe the administration of the first antibiotic dose to minimize delay in starting treatment.

Prior antibiotic therapy may mask purulent meningitis. More commonly, such chemotherapy is given in insufficient dosage and for too short a time. The patient given an injection of penicillin for a "cold" may be comatose from meningococcal meningitis on the following day. During the aseptic meningitis season patients who have a typical picture of viral meningitis may be observed closely without any additional treatment, even if they have previously received antibiotics.

Preferred treatment for adults with meningococcal or pneumococcal meningitis is penicillin G, 2 million units every 2 hours or 4 million units every 4 hours, given intravenously over a 15 minute period. If concomitant renal failure exists, the dose should be halved to avoid tremors or convulsions. Adult patients whose spinal fluid fails to demonstrate organisms on Gram staining may be treated with penicillin G if there is no reason to suspect something other than meningococcal or pneumococcal infection. In a *Haemophilus influenza* or *Listeria monocytogenes* meningitis, as well as in meningococcal and pneumococcal meningitis, intravenous ampicillin is effective. The dose should be 150 mg. per kg. per day in divided doses every 4 hours, with an initial dose of 50 mg. per kg. Ampicillin is considered by many as the drug of first choice when the bacteriology report is still pending. Intravenous therapy should be continued for the total course of treatment. Combination therapy with other antibiotics is not helpful, and may be antagonistic.⁴

For gram-negative rod meningitis, especially if hospital-acquired, a combination of systemic ampicillin, 400 mg. per kg. per day, and gentamicin in doses recommended for severe systemic infections, is a reasonable first choice of therapy pending identification and sensitivity studies. Since adequate antibacterial activity against gram-negative bacilli in the spinal fluid may not be obtained, 5 mg. of gentamicin should also be administered intrathecally every 12 hours.⁶ Firm recommendations for frequency and duration of intrathecal therapy have not been established. Penetration of many antibiotics, including both ampicillin and gentamicin, is increased with meningeal inflammation. Accordingly intrathecal administration should be continued for some days after the spinal fluid culture has become negative and the cerebrospinal fluid pleocytosis begins to resolve.

In staphylococcal meningitis, 5000 units of bacitracin may be administered intrathecally daily until the spinal fluid culture is negative. One to 2 gm. of a penicillin or cephalosporin are given intravenously every 2 to 4 hours. A penicillinase-resistant antibiotic should always be the initial therapy in patients with suspected staphylococcal meningitis.

The use of steroids in meningitis remains controversial. Since

steroids decrease cerebral edema, their use in pharmacologic dosage in selected patients with increased intracranial pressure and deterioration in mental function has been recommended. Steroids should not be used if a bacteriologic diagnosis has not been established. The patient with early tuberculous meningitis who is mistakenly thought to have a purulent meningitis, and is given a 2 week course of antibacterial therapy plus steroids, may improve initially but have subsequent progression of his meningitis.

SUMMARY

The rapid differential diagnosis of meningitis encourages prompt appropriate antibacterial therapy for pyogenic meningitis and helps the physician avoid the dangers of "shot-gun" therapy. To establish the diagnosis with dispatch, the physician must quickly evaluate many factors: the patient's age and the time of year; possible associated illnesses; presence of rashes, meningeal signs, and focal neurologic signs; and cerebrospinal fluid findings (including Gram stain, white cell count, differential white cell count, and glucose).

In aseptic meningitis peak incidence is in late summer, the symptoms are less than two weeks in duration, and there are no focal neurologic signs. Nuchal rigidity is mild to moderate. With rare exceptions the cerebrospinal fluid glucose is normal. The cerebrospinal fluid white cell count is usually 100 to 500 per cu. mm. but may be higher. The white cell differential is predominantly lymphocytic after the third day of symptoms. Polymorphonuclear cells may predominate early in the illness.

In pyogenic meningitis the patient's age, associated illness, and Gram stain of spinal fluid are most helpful in anticipating the culture results. Board-like nuchal rigidity is common. In examining the spinal fluid Gram stain, the observer should not confuse precipitated stain with bacteria. In the previously untreated patient, over 99 per cent of the leukocytes in the spinal fluid are polymorphonuclear. At times an accurate differential white cell count may be done in the counting chamber if the spinal fluid is mixed with glacial acetic acid; however, an accurate differential may require Wright's stain performed with the addition of a drop of the patient's serum. The spinal fluid glucose is characteristically less than 10 mg. per 100 ml. except in the presence of hyperglycemia.

Chronic meningitis should be suspected if the symptoms have lasted for more than 2 weeks, and if there is board-like nuchal rigidity, focal neurologic signs, and a low cerebrospinal fluid glucose. In addition to duration of illness and failure to find organisms on Gram stain, chronic meningitis is favored if the patient is not comatose, or if progression to coma has been slow. The total cerebrospinal fluid white cell count in chronic meningitis is usually less than 500 per cu. mm. Early in the course of chronic meningitis, polymorphonuclear cells may be in the majority but are usually less than 95 per cent. Furthermore, the spinal fluid glucose concentration, though low, is often greater than 10 mg. per 100 ml.

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Hyponatremic Syndromes

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The increased availability of flame photometry has led to an increase in the awareness of disorders of sodium metabolism. Hyponatremia is simply a reduction in the concentration of sodium in the serum below 135 mEq. per liter, and not a specific disease state. Interpretation of its significance depends upon the clinical setting in which it is seen.

Hyponatremia is most often described as a hypo-osmolal state. Normal serum osmolality is maintained at 290 ± 5 mOsm. per kg. serum water.³ Serum electrolytes, mainly sodium and its accompanying anions, contribute about 280 mOsm. per kg. One can estimate the serum osmolality by simply doubling the serum sodium concentration in mEq. per liter.¹ A closer approximation is available by adding in the osmolal contributions of glucose and urea nitrogen:

$$\text{Serum osmolality} = 2[\text{Na}^+] \text{ mEq./L.} + \frac{\text{glucose mg\%}}{18} + \frac{\text{BUN mg\%}}{2.8}$$

The nonelectrolytes glucose and urea together furnish about 10 mOsm. per liter except in azotemia and hyperglycemia.

BASIC CONSIDERATIONS

All body fluids are isosmotic. Cellular and extracellular osmolality are a function of osmotically active salts and water. Therefore, the approach to the clinical problems associated with hyponatremia must be prefaced by a brief review of the metabolism of salt and water.

The primary determinant of sodium excretion (First Factor) is the rate of delivery of sodium to the kidney, the glomerular filtration rate (GFR). Any change in GFR may lead to a change in sodium excretion. There is normally a balance between GFR and proximal sodium reabsorption which holds through a wide range of GFRs. However, acute de-

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creases in GFR may be accompanied by a tubular preponderance,³ that is, by reabsorption of most of the filtrate in the proximal tubule, with little sodium reaching the distal exchange site. In this situation, the urine contains little sodium or potassium. In addition to GFR, there are other intrarenal mechanisms which influence the proximal reabsorption of sodium.

Aldosterone (Second Factor) is known to exert its major action on the distal tubule, but may also increase sodium transport throughout the nephron.²⁶ An increase in aldosterone activity would lead to an acceleration of distal sodium-cation exchange, with a marked decrease in urine sodium concentration and an increase in urine potassium concentration. Potassium depletion may be clinically apparent.

Sodium balance varies with several maneuvers independent of GFR and mineralocorticoid effect which are apparent when extracellular volume is expanded. These have been collectively called Third Factor. Included in this group are physical factors as renal interstitial pressure, renal vascular resistance, renal perfusion pressure, and intrarenal plasma oncotic pressure.^{15, 22} In addition to physical factors, there is evidence that plasma from hydrated dogs leads to a natriuresis in the perfused isolated dog kidney.⁹ A natriuretic substance is said to be present in the posterior pituitary gland.⁸

In addition to these phenomena, two classical hormones, aldosterone and antidiuretic hormone (ADH), are known to respond to small variations in body volume with changes in secretory rate.

CLASSIFICATION OF HYPONATREMIAS

There are many schemes for classifying hyponatremias. One of the most useful is to divide hyponatremia into overhydrated, euhydrated, and dehydrated subgroups. This classification has the advantage of being a guide to therapy. For instance, it would not make sense to give salt and water to an individual who was overhydrated but this would be quite appropriate for a dehydrated patient.

Hyponatremia in the Overhydrated Patient

As listed in Table 1, there are a number of causes of hyponatremia in the overhydrated state. Perhaps the most well studied is the hyponatremia associated with *congestive heart failure*. Congestive heart failure with progressive edema and a decrease in serum sodium concentration carries a grave prognosis. Originally this was felt to be a consequence of salt depletion following sodium restriction and diuretic therapy. Measurement of total body sodium by the isotope dilution method demonstrated that these patients invariably had an increase in total body sodium.³¹

Renal, humoral, and cellular mechanisms have been implicated in the production of hyponatremia in congestive heart failure. As pump failure becomes more marked, GFR falls. When GFR falls to about 50 per cent of normal, most of the filtrate is reabsorbed in the proximal tubule.²⁰

Table 1. Classification of Hyponatremias

CLASS AND REFERENCE	URINE SODIUM CONCENTRATION
<i>Hyponatremia in the overhydrated patient</i>	
Congestive heart failure ³¹	↓
Cirrhosis ¹⁸	↓
Nephrotic syndrome ¹⁰	↓
Compulsive water-drinking ¹²	↓
Iatrogenic water-loading ^{25, 28}	↓
Syndrome of inappropriate ADH ^{23, 24}	↑
Renal failure ²	↑
<i>Hyponatremia in the dehydrated patient</i>	
"Salt-losing nephritis" ¹²⁷	↑
Adrenal insufficiency ²⁹	↑
Cerebral salt-wasting ¹⁹	↑
Extrarenal losses (vomiting, diarrhea, sweating) with water replacement	↓
<i>Hyponatremia in the euhydrated patient</i>	
Pseudohyponatremia, hyperlipidemia ³⁰	varies with sodium load
Pseudohyponatremia, hyperproteinemia ³⁰	varies with sodium load
Resetting of the osmostat ^{16, 17}	varies with sodium load

In this case, the final urine may have a paucity of cations, urinary sodium and potassium content both being very low. An acute change in glomerulotubular balance may change the proportionality normally found between volume of filtrate and proximal tubular reabsorption,²¹ leading to low concentrations of both sodium and potassium in the urine.

The more usual occurrence in congestive failure is a decrease in cardiac output associated with a fall in renal blood flow and alterations in intrarenal hemodynamics. This is interpreted by the macula densa as a state of volume depletion, leading to an increase in renin release by the juxtaglomerular cells, hypertensinogen degradation to angiotensin I and angiotensin II, and stimulation of aldosterone secretion. With the increase in mineralocorticoid effect, the sodium reaching the distal tubule is reabsorbed by cation exchange, leading to a urine with little sodium (<10 mEq. per liter) and an increase in potassium content (usually > 50 mEq. per liter) with a variable degree of potassium depletion.

Besides an increase in sodium reabsorption, patients with overhydration and hyponatremia have abnormalities in water metabolism. Water balance has been classically thought to be controlled by the rate of ADH secretion. The strongest stimulus controlling ADH release is the osmolality of the blood bathing the supraoptic nuclei of the hypothalamus.¹¹

A reflex arc controlling ADH release has been demonstrated in normal animals infused with saline. The diuresis can be reproduced by stretching the left atrium with a balloon, and can be blocked by cooling the vagus nerve. ADH release can be modified by a variety of maneuvers: changing blood volume or body posture, artificial respiration, and mitral

valve surgery.^{1, 6, 7} This protective diuretic reflex seems to be lost in congestive heart failure, leading to a continued ADH effect when the central volume receptors are distended.

A further cause of hyponatremia in congestive heart failure is potassium depletion associated with diuretics, secondary aldosteronism, and decreased potassium intake. The intracellular potassium deficit is partially compensated for by a shift of sodium into the cells. Correction is possible with administration of potassium chloride.¹³ The potassium enters the cells in exchange for the excess intracellular sodium, resulting in an increase in serum sodium concentration.

In summary, hyponatremia in congestive heart failure is associated with a decrease in GFR, perhaps an increase in proximal salt and water reabsorption, an increase in aldosterone secretion, and a loss of the normal left atrial stretch reflex which blocks ADH effect in volume expansion.

Therapy should be directed at the major causes by the use of absolute bed rest, cardiotonic agents, aldosterone antagonists, restriction of total fluid intake to 500 ml. per day, replacement of potassium deficits, and the use of diuretics which work primarily in the proximal portion of the nephron (furosemide and ethacrynic acid). It is occasionally helpful to increase renal blood flow with a vasodilator (e.g., theophylline) before giving the diuretics. Decreasing circulating blood volume in selected cases by venesection may increase cardiac output and lead to saluresis. Since the factors leading to hyponatremic congestive heart failure are multiple, the use of several therapeutic measures simultaneously is justified.

Hyponatremia in the *nephrotic syndrome* can be contrasted with that of congestive heart failure. In the nephrotic syndrome the marked hypoalbuminemia is associated with a fall in circulating blood volume and marked secondary aldosteronism.¹⁰ The amount of edema depends primarily upon the Starling forces across the capillary walls, and treatment should be directed at the cause of the nephrotic syndrome with treatment of the hyponatremia only if there are cerebral symptoms (*vide infra*).

Patients with *cirrhosis* and volume expansion are often hyponatremic. Although the causes of the hyponatremia have not been fully worked out, a workable explanation is as follows. Cirrhosis is a disease characterized by a decrease in what has been termed effective circulating blood volume. Although measurements of total blood volume are often normal or supranormal, the kidney acts as if the effective renal blood flow was markedly decreased, and urinary electrolyte pattern typically reflects a strong mineralocorticoid effect, with a very low sodium and a high potassium concentration.¹⁸

In congestive heart failure, nephrosis, and cirrhosis, potassium depletion may complicate the clinical picture. The causes of potassium depletion may be multiple, with vomiting, diarrhea, starvation, diuretic therapy, and secondary aldosteronism all contributing to hypokalemia. The combination of potassium loss and water retention leads to hyponatremia with overhydration. Treatment with aldosterone antagonists, po-

tassium chloride, and water restriction will often reverse the hyponatremia.

Renal failure with overhydration and hyponatremia, *compulsive water-drinking*, and salt loss with *diuretic therapy* followed by fluid replacement with water are easily diagnosed by laboratory or clinical observation. The remaining cause of hyponatremia with overhydration is the syndrome of *inappropriate secretion of antidiuretic hormone* (Table 2) first described by Schwartz's group in 1957.²³

The criteria for diagnosis have been rather carefully worked out.²⁴ These include:

1. Normal renal, adrenal, pituitary, cardiac, and hepatic function.
2. Hypo-osmolality of the extracellular fluid.
3. Formation of a urine which is less than maximally dilute and usually hypertonic to serum.
4. Continued excretion of sodium in the urine despite hyponatremia.
5. Correction of the hyponatremia by vigorous water restriction alone.

The most feared complication of hyponatremia is cerebral edema, formed as water moves into cerebral cells from the hypotonic extracellular fluid. Symptoms of water intoxication begin with anorexia, nausea, vomiting, headaches, and confusion, and proceed through personality changes, convulsions, coma, and death.¹⁴ Reversal of the symptomatology depends upon correction of the osmolal deficit throughout total body water. As the osmolality of the extracellular fluid rises, water leaves the intracellular compartment and cerebral edema subsides. The figure

Table 2. *Clinical Conditions Associated with the Syndrome of Inappropriate Secretion of Antidiuretic Hormone*

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- | | |
|------------------------|---|
| 1. Malignancy— | carcinoma of bronchus, pancreas, duodenum, thymus, prostate lymphosarcoma |
| 2. Pulmonary diseases | |
| | Bacterial pneumonia |
| | Tuberculosis |
| | Lung abscess |
| | Fungal infection |
| 3. Cerebral conditions | |
| | Head trauma |
| | Meningitis—tuberculous and bacterial |
| | Herpes simplex encephalitis |
| | Brain tumors, aneurysms |
| 4. Drugs | |
| | Sulfonylurea (chlorpropamide and tolbutamide) |
| | Polymyxin B |
| | Vincristine |
| | Thiazide diuretics |
| 5. Myxedema | |
| 6. Miscellaneous | |
| | Acute intermittent porphyria |
| | Guillain-Barré syndrome |
| | Surgical stress, anesthesia, etc. |
| | Assisted respiration |
-

given for total body water varies from author to author, but 50 per cent of body weight is a rough approximation. The correction to 290 mOsm. per liter should be done in two steps. About half the deficit should be corrected with hypertonic saline within the first 12 hours, the rest over a 24 to 48 hour period.

This correction should be precisely calculated. The patient should be weighed, the serum osmolality (or sodium concentration) noted, and the difference between the measured (or calculated) osmolality and 290 mOsm. per liter should be corrected through a volume equal to one-half the patient's weight. The use of "a little" of this solution and "some more" of that solution will not correct the hyponatremia, but often leads to progression of the central nervous system disease.

Hyponatremia in the Dehydrated Patient

The primary reason for dividing patients with hyponatremia into overhydrated and dehydrated groups is that patients who do not have congestive heart failure, cirrhosis, nephrotic syndrome, or renal failure are usually considered to have the syndrome of inappropriate secretion of antidiuretic hormone (ADH). Patients with inappropriate secretion of ADH are treated with water restriction, an approach that will lead to dire consequences in patients with adrenal insufficiency. For this reason it is extremely important that the state of hydration be carefully assayed before treatment for inappropriate secretion of ADH is undertaken. A careful examination for postural changes in blood pressure and pulse, an evaluation of tissue turgor, and investigation of an unexplained high hematocrit or low venous pressure, supplemented when indicated with a determination of blood volume, will aid in diagnosis. It must be emphasized that patients with the inappropriate secretion of ADH are not edematous, leading to potential confusion with patients who are dehydrated.

Adrenal insufficiency may be due to adrenal disease, but is seen most commonly in patients maintained on glucocorticoids who have an intercurrent illness. The diagnosis in those with a primary deficiency of adrenal steroids is made on physical examination and urinary and plasma corticoid content, while in the latter group the diagnosis is readily apparent on history.

Two groups of patients have been confused with those suffering from adrenal insufficiency: "salt-losing nephritis" and "cerebral salt-wasting." Patients with "*salt-losing nephritis*"²⁷ are believed to have glomerular preponderance, with a nephron filtration rate which is greater than tubular reabsorptive capacity, leading to salt-wasting unresponsive to mineralocorticoid treatment. Replacement of deficits and maintenance on a high salt and water intake is the obvious treatment of this condition.

About 20 years ago, Peters¹⁹ reported a group of patients with *cerebral salt-wasting*, who were dehydrated and resistant to steroid therapy. These patients had a self-limited disease, but required large volumes of salt and water until the disorder passed.

Patients with extrarenal loss of salt and water (diarrhea, vomiting, or

sweating) with water replacement may also present as dehydrated patients with hyponatremia.

In the patients with adrenal insufficiency, "salt-losing nephritis," and "cerebral salt-wasting," hyponatremia will coexist with a sodium-rich urine of rather high osmolality. Correction with salt will be transient, with a rapid return to the hyponatremia state upon discontinuance of saline. The possibility of confusion with inappropriate secretion of antidiuretic hormone cannot be overemphasized when discussing the volume-depleted patient.

Hyponatremia in the Euhydrated Patient

There are several instances when hyponatremia may exist in the normally hydrated patient with no derangement of water and sodium metabolism. Sodium is present in *serum water*, but is expressed in terms of *serum volume*. Therefore, a substance that is present in serum but does not contain sodium will produce a pseudohyponatremia. Two disease states have been described with pseudohyponatremia, the hyperlipidemias and the hyperproteinemias.

Serum water has been estimated by using the mean specific volume of total lipids (1.03) and total proteins (0.73), as in the following formula:³⁰

$$Ws = 99.1 - 1.03 Ls - 0.73 Ps$$

where Ws = ml. of water in 100 ml. of serum

99.1 = volume of serum minus crystalloids (nonlipid, nonprotein solids)

Ls = total lipid concentration in gm./100 ml. of serum

Ps = total protein concentration in gm./100 ml. of serum

and $\text{Corrected serum Na (in mEq./L. of serum water)} = \text{observed Na} \times 100/Ws$, with normal being 148 to 163 mEq./L.

Another cause of hyponatremia with euhydration is the *resetting of the osmostat*. Two patients have been described who responded to variations in salt and water intake in a perfectly appropriate fashion but who had fixed hyponatremia in the range of 125 mEq. of sodium per liter of serum. One of these patients had tuberculosis¹⁶ and the other had a massive cerebrovascular accident.¹⁷

CONCLUSIONS

Hyponatremia has diverse etiologies and treatments. The response of a normal person with hyponatremia after volume loss and water replacement is to decrease sodium excretion to a minimum (< 10 mEq. per liter). Because of the basic pathophysiologic mechanisms involved, patients with congestive heart failure, cirrhosis, and nephrotic syndrome conserve salt and water as if they were dehydrated.

Hyponatremia with saluresis has a limited diagnostic spectrum

(Table 1). The possibilities are: renal failure, adrenal insufficiency, cerebral salt-wasting, or inappropriate secretion of antidiuretic hormone. Thus, dividing patients with hyponatremia according to volume status or presence of sodium in the urine leads to the same conclusion, that individuals with hyponatremia and salt-losing are dehydrated or have inappropriate secretion of antidiuretic hormone.

Presupposition that inappropriate secretion of antidiuretic hormone is the diagnosis will lead to planned volume restriction, a course fraught with danger to the dehydrated patient with a salt-losing disease.

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Hypokalemia and Hyperkalemia

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Potassium represents the major cation of intracellular fluid. While intracellular potassium concentration is normally about 150 mEq. per liter, the concentration of potassium in plasma and extracellular fluid normally varies over a narrow range, from 3.5 to 5.0 mEq. per liter. The large gradient of potassium concentration across cell membranes and the reciprocal gradient for sodium ion concentration are maintained by the active transport of potassium into and sodium out of cells; this transport is mediated largely by cell membrane ATPase. The precise concentration gradient for potassium between the intracellular and extracellular fluid can be influenced by the pH of the extracellular fluid, possibly by aldosterone, and by alterations in the permeability of cell membranes to potassium and sodium and the metabolic integrity of the membrane sodium-potassium pump.

While extracellular potassium constitutes only about 1 per cent of the total body potassium content, changes in extracellular potassium concentration, both hypokalemia and hyperkalemia, represent serious and often life-threatening clinical conditions. This paper will attempt to review the pathogenesis, manifestations, and treatment of some of these disorders in potassium homeostasis.

HYPOKALEMIA

Total body potassium homeostasis requires that the urinary excretion of potassium equal the total dietary potassium intake. Fecal and sweat excretion of potassium is usually negligible, except in diarrheal states.

The precise mechanism whereby renal potassium excretion responds to changes in dietary potassium intake is unclear. Experimental animals fed a diet high in potassium demonstrate enhanced renal excretion and tissue uptake of a parenterally administered potassium load.¹ This effect may be due in part to increased aldosterone production during high potassium feeding.² Since the kidneys in man (and most other species) cannot

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elaborate potassium-free urine, marked reduction in potassium intake can result in total body potassium depletion because of continued urinary losses of potassium.¹ More commonly, in disease states, potassium depletion results from excessive loss of potassium through either the gastrointestinal tract or the kidney.

Gastric juice contains 8 to 10 mEq. of K^+ per liter; the concentration of potassium in pancreatic and jejunal secretions is somewhat higher. In patients with protracted vomiting or external gastrointestinal drainage, cumulative potassium losses may be considerable and lead to potassium depletion and ultimately, hypokalemia. Alkalosis, consequent to the loss of hydrogen ion in gastric secretions, contributes significantly to the development of hypokalemia through two additional mechanisms. First, in the presence of extracellular alkalosis, potassium ions migrate from extracellular to intracellular fluid. Second, and quantitatively more important, since the hydrogen ion and the potassium ion appear to compete at a common exchange site for sodium in the distal renal tubule,³ alkalosis results in increased urinary loss of potassium which may persist despite severe potassium depletion and hypokalemia. Chronic diarrheal states and prolonged laxative abuse may result in potassium deficiency through gastrointestinal loss.¹²

The urinary excretion of potassium results almost exclusively from secretion of this ion in the distal renal tubule, virtually all of the filtered potassium having been reabsorbed proximally. Distal tubular potassium excretion occurs in exchange for sodium and is stimulated by aldosterone and other mineralocorticoid hormones. Excessive potassium excretion and hypokalemia may be expected when sodium is presented to the distal tubule exchange site and sodium-potassium exchange is accelerated by increased mineralocorticoid hormone activity. Thus, in primary aldosteronism, whether due to adrenocortical adenoma or bilateral adrenal hyperplasia, potassium depletion and hypokalemia are almost invariably observed while patients are receiving a normal diet. Low salt diet, by decreasing the amount of sodium available at the distal tubule exchange site, may result in decreased potassium loss and mask this evidence of aldosterone excess. Aldosterone antagonists, such as spironolactone, competitively inhibit the tubular action of aldosterone and may reverse all the biochemical sequelae of aldosterone excess.⁵

In contrast to primary aldosteronism, patients with sodium-retaining edematous states such as nephrotic syndrome, congestive heart failure, and hepatic cirrhosis (secondary aldosteronism) rarely manifest hypokalemia unless given diuretics. Indirect evidence suggests that in these states of "secondary aldosteronism" sodium reabsorption is almost complete in portions of the nephron proximal to the site of sodium-potassium exchange.⁸ Despite increased aldosterone secretion, excessive potassium loss does not occur, because of the relative unavailability of sodium at the distal exchange site. Only when diuretic agents are administered and block more proximal reabsorption of sodium does potassium excretion become excessive and hypokalemia ensue. This form of diuretic-induced hypokalemia may be prevented by administration of drugs which block distal sodium-potassium exchange either by competitive inhibition of aldosterone (spironolactone) or directly (triamterene).

Hypokalemia is a feature of Bartter's syndrome, which is characterized by juxtaglomerular cell hyperplasia, excess secretion of renin and aldosterone, hypokalemia, and normal blood pressure.² While this syndrome was initially attributed to vascular unresponsiveness to angiotensin II and consequent juxtaglomerular hyperplasia, more recent studies suggest that impaired proximal sodium reabsorption might result in increased delivery of sodium to the distal nephron with consequent sodium and potassium loss and secondary stimulation of the renin-angiotensin-aldosterone system.⁹

Hypokalemia attributable to excessive urinary loss of potassium is also a feature of renal tubular acidosis. In untreated renal tubular acidosis, the urinary loss of sodium, a result of failure to reabsorb bicarbonate in the proximal tubule ("proximal" or Type II renal tubular acidosis) or failure to exchange hydrogen for sodium in the distal tubule ("distal" or Type I renal tubular acidosis), results in secondary aldosteronism and persistent potassium loss.¹¹ While potassium loss is usually corrected by administration of sodium bicarbonate in the classic or distal variety of renal tubular acidosis, potassium-losing may persist despite correction of acidosis in the proximal forms.

The clinical manifestations of hypokalemia include muscle weakness, decreased smooth muscle contractility manifested as paralytic ileus, cardiac arrhythmias, and hypokalemic nephropathy with moderate proteinuria, impaired concentrating capacity, and (in some instances) impairment of glomerular filtration. Estimation of the amount of potassium required for correction of hypokalemia is largely empiric; in most clinical settings, hypokalemia reflects a considerable loss of intracellular potassium, often ranging from 300 to 500 mEq. If there is coincident alkalosis, favoring shift of potassium into cells, the total deficit may be less than this estimate, while in the presence of systemic acidosis, the deficit may be greater than this estimate. Hypokalemia is often associated with gastrointestinal loss of hydrogen ion, resulting in metabolic alkalosis. Recent studies have demonstrated that alkalosis, associated with decreased plasma chloride and increased plasma bicarbonate concentrations, results in the delivery of increased concentrations of poorly reabsorbable anion (bicarbonate) to the distal tubule and continued hydrogen ion and potassium secretion despite potassium administration.¹³ Correction of potassium deficiency in this circumstance requires concomitant administration of chloride ion.¹³ In the presence of alkalosis, potassium should be administered as the chloride salt rather than as acetate, bicarbonate, or citrate salts.

HYPERKALEMIA

In most instances hyperkalemia results from impaired renal excretion of this ion. Since potassium excretion is largely accomplished by tubular secretion rather than glomerular filtration, hyperkalemia does not usually supervene in the course of progressive renal disease until the glomerular filtration rate is very markedly reduced and clinical signs of uremia are prominent. Patients with reduced renal function have re-

duced ability to handle potassium loads, and striking hyperkalemia may result from inadvertent administration of potassium in the form of salt substitutes or low-sodium dietetic food.

An exception is the occurrence of hyperkalemia, often in association with hyperchloremic acidosis, in some patients with chronic pyelonephritis. Lathem¹⁰ and Carroll and Farber⁷ described striking hyperkalemia in such patients despite only mild degree of impairment in glomerular filtration and proposed that there was a defect in cellular uptake of potassium. Other investigators have observed selective decrease in aldosterone production (that is, reduced aldosterone production with normal corticosteroid secretion) in patients presenting similar clinical features of hyperkalemia, hyperchloremic acidosis, and only moderate impairment in glomerular filtration, and have attributed hyperkalemia and metabolic acidosis to mineralocorticoid deficiency.¹¹

Hyperkalemia from impaired potassium excretion may be due to specific impairment of distal tubular potassium excretion. Distal potassium excretion is regulated by mineralocorticoid hormones, predominantly aldosterone. Mineralocorticoid deficiency, which may be selective—as described above and in some children who appear to lack the zona glomerulosa enzyme, 18-hydroxylase, which is required for aldosterone biosynthesis—or part of generalized adrenocortical insufficiency, is often manifested by increased extracellular potassium concentration. Hyperkalemia has also been observed in patients receiving therapeutic doses of the aldosterone inhibitor, spironolactone.

Considering the very large reservoir of intracellular potassium which exists in dynamic equilibrium with potassium in extracellular fluid, it is remarkable that hyperkalemia resulting from a shift of potassium out of cells is not a more frequent event. In light of the fact that the daily intake of potassium often approximates the total quantity of potassium in the extracellular fluid compartment, the capacity of the cells to rapidly take up potassium and thereby maintain extracellular K^+ concentration in the very narrow range compatible with normal membrane function is even more remarkable. This fine regulation is most often disturbed by changes in acid-base balance. Metabolic acidosis may result in the rapid, often lethal development of very profound hyperkalemia. In the rare, poorly understood disorder of familial hyperkalemic periodic paralysis, elevated plasma potassium concentration is similarly attributable to a shift of potassium from cells to the extracellular fluid space.

Hyperkalemia is clinically manifested by profound muscular weakness and disturbances of cardiac conduction. The treatment of hyperkalemia requires reduction of the intake of potassium along with measures designed to increase the elimination of potassium. Where renal function is adequate, renal potassium excretion may be augmented by administration of diuretic agents such as thiazides, ethacrynic acid, or furosemide which results in increased presentation of Na^+ to the distal exchange site. More commonly it is necessary to remove potassium by administration of ion exchange resins via the gastrointestinal tract (orally or per rectum). These resins, usually in the sodium or ammonia phase, bind potassium in the lumen of the gastrointestinal tract and can ac-

comply considerable potassium removal. Peritoneal dialysis and hemodialysis have been employed when hyperkalemia is severe and life-threatening and rapid correction of this abnormality is desirable. The intravenous administration of glucose and insulin causes potassium to enter cells and may effect a rapid decrease in extracellular potassium concentration. When severe metabolic acidosis coexists with hyperkalemia, a dramatic reversal of the elevation in serum K^+ and the attendant muscular weakness and/or electrocardiographic changes may be achieved almost instantly by the infusion of alkali (sodium bicarbonate) and correction of acidosis. When hyperkalemia can be shown to be attributable to mineralocorticoid deficiency, rapid correction of this disturbance can be achieved by administration of exogenous mineralocorticoid such as 9- α -fluorohydrocortisone.

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Fasting Hypoglycemia

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In our culture adults and older children eat three meals a day. Our intermediary metabolism is therefore impressed into a mold with two divisions: fed and fasting. These divisions are especially useful when considering the metabolism of glucose. The fed state for this carbohydrate exists for about 3 hours after each meal, or one third of the day; for two thirds of every day we are in a fasting state. Claude Bernard observed that constancy of the internal environment is the condition of free and independent existence. We know that blood glucose concentration plays an important role in this constancy: it must be maintained during the fasting two-thirds of each day or existence itself is threatened. How it is maintained—how we prevent hypoglycemia during this recurring fast—is an important theme of this article, which is concerned with conditions that overcome glucose homeostatic mechanisms and cause fasting hypoglycemia.

MAINTAINING FASTING BLOOD GLUCOSE

Normoglycemia depends on a continual balancing of the amounts of glucose entering and leaving the blood. The processes that regulate this balance are shown in Figure 1. Fasted or fed, body tissues continue to remove glucose from blood and use it for energy needs, for synthesis of other molecules, and for storage (right panel). When glucose is not available from food sources, its inexorable consumption by tissues is balanced by two processes that add glucose to blood: gluconeogenesis and glycogenolysis (left panel). The liver, under potent hormonal influences, is the fulcrum of glucose homeostasis. It has well-developed mechanisms for synthesis of glucose from noncarbohydrate precursors (gluconeogenesis), and for breakdown of stored glycogen to glucose (glycogenolysis) which is free to re-enter the blood.

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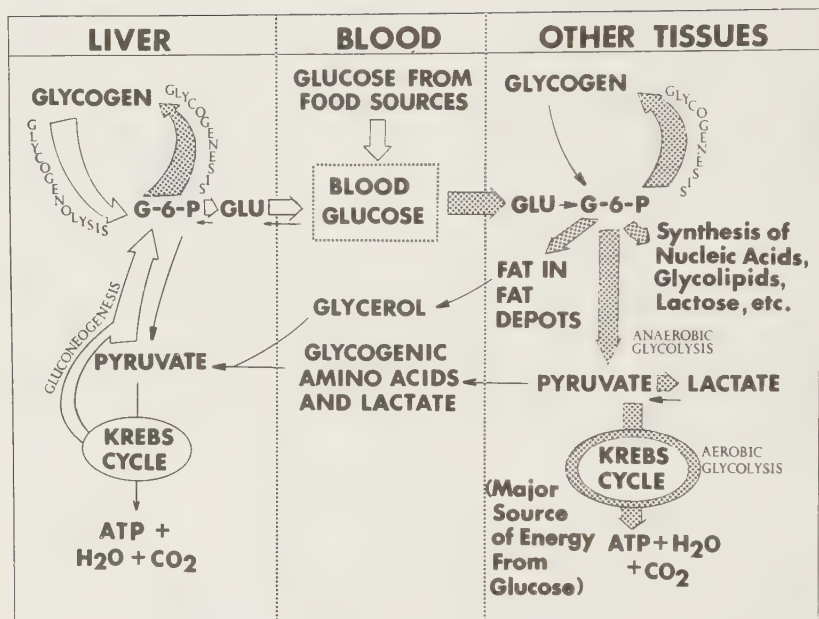


Figure 1. General scheme of processes controlling blood glucose concentration. Large white arrows indicate processes adding glucose to blood, large shaded arrows those removing glucose from blood.

Gluconeogenesis (Fig. 2) comprises the synthesis of glucose from lactate, pyruvate, glycerol, odd-chain fatty acids, and most amino acids. The major source of carbon for the net formation of glucose is pyruvate, derived mainly from transamination of amino acids. Quantitatively, amino acids are the major substrates for gluconeogenesis, and alanine appears to be the major amino acid (Fig. 2, reactions 25, 26).³ It is the principal amino acid extracted by the liver from the splanchnic circulation in both post-absorptive and prolonged fasting states; its output from resting muscle exceeds that of all other amino acids; and alone among the amino acids, it is *increased* in blood during exercise, probably because of increased synthesis from pyruvate during glycolysis.³ To help explain its primacy as a gluconeogenic precursor, some workers have recently proposed an important metabolic cycle for alanine (Fig. 3).^{5, 18}

Gluconeogenesis is controlled by complex mechanisms, some of which are diagrammatically shown in Figure 2. Hormones have important effects on these mechanisms. Glucocorticoids, catecholamines, and glucagon stimulate gluconeogenesis and raise fasting blood glucose levels; insulin inhibits gluconeogenesis and lowers fasting blood glucose. Table 1 outlines these and other effects of hormones on processes involved in controlling blood glucose. During the usual post-absorptive period and short-term fasts the liver accounts for about 80 per cent of glucose produced by gluconeogenesis, and the kidneys for 20 per cent. During prolonged starvation the kidneys contribute half of the glucose synthesized.

Glycogenolysis. The quantity of liver glycogen remains fairly constant in animals with continual access to food; yet there is unceasing formation and degradation of this complex, highly branched polysaccharide (Fig. 4). During a fast the degradation process, glycogenolysis, predominates: livers of animals fasted for 24 hours are virtually depleted of glycogen. (We stress liver glycogen—not muscle, brain, or heart glycogen—as a major source of blood glucose, because of these organs only the liver has large quantities of glucose-6-phosphatase, which catalyzes formation of free glucose from G-6-P [Fig. 4, reaction 4]. In other tissues, glycogenolysis results in increased intracellular glycolysis, meeting energy requirements of these tissues without liberating free glucose.) Transient or trivial requirements for glucose production may be met by glycogenolysis, but when the need is prolonged or quantitatively great gluconeogenesis is indispensable for maintaining an adequate blood glucose level.

Liver glycogen formation and breakdown are regulated by hormones, as noted in Table 1. It should be mentioned that a decline in plasma insulin and rise in plasma glucagon are normal concomitants of fasting, and account for the overall changes observed in liver glycogen (increased glycogenolysis) at this time.

FASTING HYPOGLYCEMIA

The causes of this are legion, and are discussed in detail elsewhere.^{2, 20, 26} A glance at Table 2 should convince the reader that the con-
(Text continues on p. 1450)

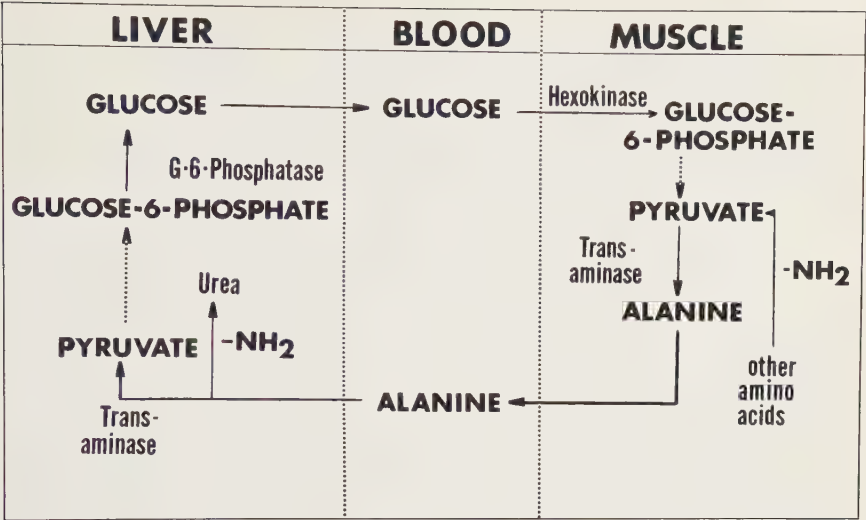


Figure 3. The alanine cycle and gluconeogenesis.¹⁸ One reason that alanine appears to be the major amino acid involved in gluconeogenesis is its large output—exceeding that of all other amino acids—from muscle into blood. This allows its 3-carbon skeleton to serve as substrate for conversion to pyruvate and glucose in the liver. Unidirectional arrows indicate proposed direction of net flow, not irreversibility.

Figure 2. Gluconeogenesis. The key enzymatic steps that reverse glycolysis and allow formation of glucose are shown by large shaded arrows. The liver and kidney are the only organs containing fructose-1-6-diphosphatase (reaction 7) and glucose-6-phosphatase (reaction 1), which are essential for production of free glucose. Major gluconeogenic substrates are enclosed in rectangles. Alcohol metabolism, with its consumption of NAD, is indicated in the circle. Note emphasis on NAD-dependent gluconeogenic reactions (thick black arrows) suppressed by alcohol metabolism (see Case 5). Enzyme code for the reactions:

- | | |
|--|---|
| 1. Glucose-6-phosphatase | 14. Pyruvate kinase |
| 2. Glucokinase + Hexokinase | 15. Pyruvate carboxylase |
| 3. Galactokinase | 16. Phosphoenol pyruvate carboxykinase |
| 3a. Phosphogalactose uridyltransferase | 17. Pyruvate dehydrogenase complex |
| 3b. UDP-Galactose epimerase | 18. Malic enzyme |
| 4. Phosphoglucomutase | 19. Isocitrate dehydrogenase |
| 4a. Glucose-6-P dehydrogenase | 20. α -ketoglutarate dehydrogenase |
| 5. Phosphohexose isomerase | 21. Malate dehydrogenase |
| 6. Phosphofructokinase | 22. Lactate dehydrogenase |
| 7. Fructose-1-6-diphosphatase | 23. Alcohol dehydrogenase |
| 8. Aldolase | 24. Acetaldehyde dehydrogenase |
| 8a. Triose-P-isomerase | 25. Alanine dehydrogenase |
| 9. α -Glycero-P dehydrogenase | 26. Transaminase |
| 10. Glycerokinase | 27. Glutamate dehydrogenase |
| 11. Glyceraldehyde-3-P dehydrogenase | 28. Fatty acid β -oxidation |
| 12. Fructokinase | 29. Non-oxidative deamination + complex multistep pathway |
| 13. Fructose-1-P aldolase | |

Table 1. *Effects of Cyclic AMP and Certain Hormones on Processes Controlling Blood Glucose Concentration*

SUBSTANCE	NET EFFECT			
	GLUCONEOGENESIS	GLYCOGENESIS	GLYCOGENOLYSIS	PERIPHERAL UTILIZATION OF GLUCOSE
Cyclic AMP	Stimulates	Inhibits	Stimulates	?
	Increases Pyruvate → oxalacetate → phosphoenolpyruvate	Reverses activation of hepatic glycogen synthetase	Converts inactive liver phosphorylase kinase to active kinase → activates phosphorylase	INSULIN SECRETION
Insulin	Inhibits	Stimulates	Inhibits	Stimulates
	1. Reduces amino acid intake by liver 2. Suppresses protein catabolism and amino acid supply to liver 3. Suppresses pyruvate → oxalacetate → phosphoenolpyruvate	1. Increases glu- cose → Glu-6-P by stimulating glucokinase activity 2. Activates hepatic glycogen synthetase	Decreases activity of liver phosphorylase kinase, via sup- pression of adeny- l cyclase system	Decreases
Cortisol	Stimulates	Stimulates	Inhibits	Inhibits
	1. Increases flow of substrates to liver 2. Required for activat- ing gluconeogenic actions of glucagon and epinephrine	Activates hepatic glycogen synthetase	An early action of injected cortisol on glucose metabolism; decreases insulin- stimulated glucose uptake	Increases

Glucagon	3. Increases synthesis of certain gluconeogenic enzymes				
	<i>Stimulates</i>	<i>Inhibits</i>	<i>Stimulates in liver only</i>	<i>?</i>	<i>Increases</i>
	Increases pyruvate → oxalacetate → phosphoenolpyruvate	Reverses activation of hepatic glycogen synthetase	Increases activity of liver phosphorylase kinase, via adenylyl cyclase system		Stimulates adenylyl cyclase system → increased formation of cyclic AMP in pancreatic beta-cells
Epinephrine	<i>Stimulates</i>	<i>Inhibits</i>	<i>Stimulates in liver and muscle</i>	<i>Inhibits</i>	<i>Increases</i>
	1. Increases flow of substrates to liver 2. Increases pyruvate → oxalacetate → phosphoenolpyruvate	Reverses activation of hepatic glycogen synthetase	Increases activity of liver and muscle phosphorylase kinase, via adenylyl cyclase system		Inhibits
Growth hormone	<i>?</i>	<i>Stimulates in muscle and heart</i>	<i>?</i>	<i>Inhibits</i>	<i>Increases</i>
	1. Decreases supply of amino acids to liver; possible inhibition. 2. Increases supply of fatty acids to liver; possible stimulation.	No known action on hepatic glycogen synthetase		<i>Inhibits (acute—hours)</i> <i>Stimulates (chronic—days)</i>	These are experimental effects of insulin response to glucose after growth hormone injection

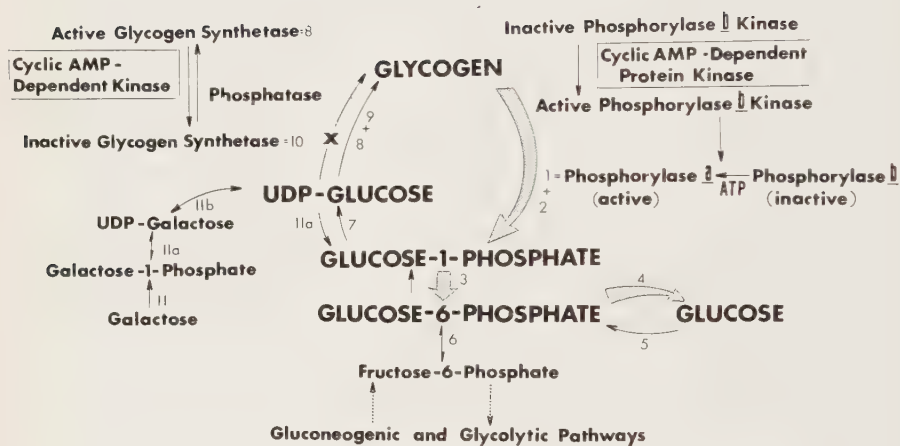


Figure 4. Glycogenolysis and glycogenesis. The key enzymatic steps that catalyze glycogen degradation and formation of glucose are shown by large shaded arrows. Of the major glycogen-containing organs only the liver contains glucose-6-phosphatase (reaction 4) which is essential for formation of free glucose. Enzyme code for the reactions:

- | | |
|---|--|
| 1. Hepatic phosphorylase <i>a</i> | 8. Active glycogen synthetase (UDPG-transferase) |
| 2. Amylo-1,6-glucosidase (Debranching enzyme) | 9. Amylo-(1,4 → 1,6) transglucosidase (Branching enzyme) |
| 3. Phosphoglucomutase | 10. Inactive glycogen synthetase |
| 4. Glucose-6-phosphatase | 11. Galactokinase |
| 5. Hexokinase | 11a. Galactose-1-P uridyl transferase |
| 6. Phosphohexose isomerase | 11b. UDPG-pyrophosphorylase |
| 7. UDPG-pyrophosphorylase | |

Table 2. *Causes of Fasting Hypoglycemia*

1.	Insulinomas
	a. Solitary or multiple adenomas
	b. Carcinoma
	c. Associated with syndrome of multiple endocrine adenomata
2.	Other endocrine diseases
	a. Hypopituitarism
	b. Isolated ACTH deficiency
	c. Isolated growth hormone deficiency
	d. Addison's disease
	e. Enzymatic defects of glucocorticoid synthesis
	f. Myxedema coma
3.	Small epithelioid tumors derived from foregut anlage
	a. Islet tumor with production of insulin and 5-hydroxytryptophan, gastrin, or corticotropin
	b. Insulin-producing carcinoid tumors of gut or bronchus
4.	Massive extrapancreatic tumors
	a. Mesenchymal tumors
	b. Adrenocortical carcinoma
	c. Hepatoma
	d. Gastrointestinal carcinoma
	e. Wilms' tumor
5.	Liver disease
	a. Fulminant liver necrosis (viral, toxic)
	b. Severe chronic passive congestion
	c. Terminal phase of cirrhosis
	d. Severe malnutrition
6.	Hepatic glycogenoses: Types I, III, VI, VII
7.	Alcohol-induced hypoglycemia*
8.	Drug-induced hypoglycemias*
	a. Insulin administration
	b. Hypoglycemic sulfonylureas
	c. Miscellaneous (salicylates, antihistamines, THAM, para-aminobenzoic acid, haloperidol, propoxyphene)
9.	Hypoglycemias of infancy and early childhood
	a. Neonatal hypoglycemias
	b. Idiopathic hypoglycemia of childhood
	c. Familial leucine sensitivity
	d. Ketotic hypoglycemia
	e. Drug-induced hypoglycemias*
	I. Neonatal: Maternal ingestion of sulfonylureas
	II. Infancy: Salicylates
	III. 2 to 6 years: Alcohol

*Indicates induced-fasting hypoglycemias

cept embodied in "Dx: hypoglycemia; Rx: glucose," is inadequate and can be dangerously wrong in practice, for hypoglycemia (a chemical finding, not a diagnosis) often reflects a serious underlying disorder. And glucose therapy—though necessary, and sometimes lifesaving—may not be sufficient: it is often not definitive therapy for the underlying disorder.

Symptomatic hypoglycemia is usually found in adults when the true blood glucose concentration falls to 40 mg. per 100 ml. or less (equivalent to blood sugar levels of 50 to 60 mg./100 as measured by the Autoanalyzer), or when there is a rapid decline from hyperglycemia to normal blood glucose concentration. The symptoms, often similar regardless of etiology, are due to hypoglycemic stimulation of the sympathetic portion of the autonomic nervous system, and depression of the central nervous system (neuroglycopenia). Increased activity of the autonomic nervous system accounts for pallor, sweating, anxiety, tremulousness, pupillary dilatation, and tachycardia. Cortical depression accounts for confusion, personality changes, memory defects, and psychotic thinking and behavior that may dominate the clinical picture. Subcortical, mesencephalic, and myelencephalic depression account for loss of consciousness, primitive movements, tonic spasms, and deep coma that may—within hours—cause permanent brain damage or death.

The cases that follow have been selected because they illustrate important aspects of pathophysiology, clinical presentation, and treatment of fasting hypoglycemia in adult patients.

INSULINOMA

Case 1. Multiple Endocrine Adenomata

F.S., a 30 year old woman, complained of episodes of sweating, nervousness, diplopia, confusion, incontinence, amnesia and, on a few occasions, unconsciousness. The attacks most often occurred on weekends when she awoke late for breakfast. An attack could be aborted by drinking fruit juice. On one occasion the patient was admitted to a psychiatric institution because of bizarre behavior and was diagnosed as being schizophrenic.

The patient had amenorrhea since her early teens. She had passed urinary calculi on two occasions. No members of her family had a history of endocrine disease, bizarre behavior, or renal stones.

Laboratory evaluation demonstrated hypercalcemia, a typically diabetic glucose tolerance test (fasting 67 mg. per 100 ml.; 1 hr., 192; 2 hr., 217; 3 hr., 210), and enlargement and erosion of the sella turcica. Hypoglycemia (30 mg. per 100 ml.) was produced by a 24 hour fast.

The combination of fasting hypoglycemia, hypercalcemia, and pituitary tumor established a diagnosis of multiple endocrine adenomata. Therapy consisted of removal of two insulinomas in the distal pancreas, removal of two parathyroid adenomas, and radiation therapy of the pituitary tumor.

Case 2. Solitary Insulinoma

A. S., a 59 year old woman, was in excellent health until 4 months before evaluation. At that time she was involved in a minor automobile accident as a result of her "poor judgment." Before breakfast 6 days later the patient had an episode of confusion that was relieved by food. That evening she was found standing in front of a window, sweaty and unresponsive to questions. The symptoms were relieved by drinking juice.

Because of recurrent bizarre behavior the patient was evaluated by a neurologist. No abnormal findings were noted on brain scan, EEG, or lumbar puncture, and skull films were normal. Although evaluation was incomplete, the patient requested discharge. The neurologist noted a blood sugar of 43 mg. per 100 ml. at the fifth hour of an oral glucose tolerance test. The reported results were: Fasting, 50 mg. per 100 ml.; $\frac{1}{2}$ hr., 128; 1 hr., 147; 2 hr., 167; 3 hr., 132; 4 hr., 52; and 5 hr., 43. No symptoms were noted during the test.

Following discharge, the patient was referred by her son, a physician, to the endocrine unit. In view of the history suggestive of fasting hypoglycemia, a tolbutamide tolerance test was performed. The patient's fasting blood sugar was 74 mg. per 100 ml., and following 1 gm. of intravenous tolbutamide the level of blood sugar fell progressively: $\frac{1}{2}$ hr., 44; 1 hr., 28; 2 hr., 24; 3 hr., 29. Fasting serum insulin level was 79 microunits per ml. (normal less than 25). The level rose to more than 200 at 30 minutes, and remained greater than 200 microunits throughout the rest of the test. Although the blood sugar remained less than 40 per cent of the fasting level at three hours, the patient appeared normal and answered questions. She was not sweaty or nervous, and had neither tachycardia nor dilatation of the pupils. However, when asked to read a simple set of directions and explain what had been read, she was unable to do so. The test results were consistent with a diagnosis of insulinoma. An abdominal exploration was performed and a single adenoma removed. The patient has been symptom-free since surgery.

Patients with insulinoma often experience recurrent autonomic and neuroglycopenic symptoms separated by periods of well-being. Neuroglycopenia predominates: the bizarre behavior leading to psychiatric hospitalization, the poor driving judgment, and the episodes of amnesia or unconsciousness that punctuated our patients' histories are common-place in this disorder. Since hypoglycemic symptoms appear to be related to the rate of fall of blood glucose—a rapid decrease being associated with autonomic stimulation, a slower fall with central nervous system depression—the predominance of cortical and subcortical dysfunction in insulinoma is understandable. Interestingly, relief of symptoms by juice, fruit, or other food may be known to some patients (or their relatives), and may provide the initial clue to the diagnosis.

Routine glucose tolerance tests are sometimes used diagnostically in patients with fasting hypoglycemia. The results are rarely diagnostic, and are often misleading. This is particularly true for patients with insulinomas, who notoriously lack insulin-secreting sensitivity to glucose loads despite (or possibly because of) elevated serum insulin levels while fasting. Normal people have low fasting insulin levels with spurts of pancreatic insulin secretion after eating. During the fed state in the normal individual, serum levels of insulin are often higher than those found in patients with insulinomas. Both our patients had diabetic glucose tolerance. This can be accounted for by three mechanisms. First, the insulin-secreting tumor cells were at least partly refractory to glucose stimulation. Second, the normal pancreatic islet cells, already suppressed by the hypoglycemia induced by tumor insulin, failed to respond to the glucose stimulus. Finally, compensatory secretion of hyperglycemic hormones, already present in the fasting state, may have contributed to excessive hyperglycemia induced by the glucose load. In summary, the inappropriate secretion of insulin by islet cell tumors is capable of producing alarming hypoglycemia in the fasted state but is sometimes inadequate to prevent abnormal hyperglycemia during a glucose tolerance test—espe-

cially in the presence of suppressed normal islet cells and continued secretion of hormones that oppose insulin's hypoglycemic actions.

Fasting hypoglycemia has many etiologies (See Table 2). The diagnosis of insulinoma requires that hypoglycemia in the presence of hyperinsulinemia be demonstrated. Approximately 90 per cent of insulinoma patients will have serum insulin levels that are elevated for the corresponding blood sugar after a 12 hour fast. If hypoglycemia alone is used as the diagnostic test, two thirds of insulinoma patients will experience symptoms between the twelfth and twenty-fourth hours of a fast. Few will be able to tolerate a 48 hour fast. Serum insulin levels in fasted subjects are more sensitive and specific than glucose levels or clinical symptoms in determining the existence of an insulinoma.

The intravenous administration of 1 gm. of tolbutamide to patients with suspected insulinoma has proven to be a reliable diagnostic tool. It takes advantage of the increased sensitivity of insulin secretion to tolbutamide found in insulinoma patients. Typically in these patients blood sugar levels fall and remain below 65 per cent of the fasting level at 3 hours after tolbutamide administration. In addition, serum insulin levels are often elevated above 150 microunits per ml. at some time during the test. In normal subjects, blood sugar returns to more than 65 per cent of the fasting level by 3 hours, and serum insulin does not reach the level associated with insulinoma.

The syndrome of multiple endocrine adenomata should be considered in any patient with an endocrine gland tumor that secretes a polypeptide hormone. Endocrine cells destined to produce such hormones are apparently derived from a single line of neuroectodermal cells which migrate from the neural crest to the primitive gut.³⁰ These cells enter into gut outpouchings destined to form various endocrine organs. They may also give rise to cells that will eventually produce the gut hormones secretin, cholecystokinin, serotonin, pancreaticozym, and gastrin. A genetic defect causing dysplasia of the neural ectoderm may be responsible for the syndrome of multiple endocrine adenomata which is often familial.³⁰

Therapy for benign insulinoma is surgical resection of the tumor or resection of a major portion of the pancreas if there are multiple tumors. In cases with metastatic deposits that cannot be resected, diazoxide or the anti-tumor agent streptozotocin, which inhibit insulin secretion, have proven helpful. If the multiple endocrine adenomata syndrome is present, the other endocrine organs involved should be treated as indicated. In view of the frequency of hypercalcemia resulting from recurrent parathyroid adenomas, the removal of 3 to 3½ parathyroids is indicated even when a single adenoma is found at neck exploration.

ADRENAL INSUFFICIENCY

Case 3. Isolated ACTH Deficiency

F. P., a 54 year old janitor, was admitted unconscious to Queens Hospital Center. He had gone to work early in the afternoon and was found lying uncon-

initial fever disappeared on the first hospital day. After testing, treatment was begun with cortisol, 10 mg. orally every 8 hours. He had normal blood sugars and was alert, cooperative, and 12 lb. heavier when discharged 6 weeks after admission.

Adrenocortical insufficiency was considered in this man because his acute episode of hypoglycemia was accompanied by chronic weight loss, anorexia, weakness, and irritability. The ultimate cause of these findings, isolated ACTH deficiency, was demonstrated by low urinary 17-hydroxy-steroid excretion that improved after exogenous ACTH but not after metyrapone, and normal blood or urine levels of other pituitary hormones (Table 3).

Hypoglycemia is a life-threatening complication of all forms of adrenal insufficiency, primary or secondary. This fact is best appreciated when the multiple effects on blood glucose of cortisol are considered (Table 1). The net effect on the actions of this major glucocorticoid on normal fasting subjects is to maintain blood glucose levels by stimulating gluconeogenesis, and to replenish glycogen stores by stimulating hepatic glycogen synthetase activity (Fig. 4, reaction 8). Perhaps the single most important effect of cortisol on gluconeogenesis is its catabolic action on muscle and other extrahepatic tissues. It is this action which increases the flow of amino acids—quantitatively the major substrates of gluconeogenesis—to the liver, and makes them available for transformation to glucose (Fig. 2, reactions 25–27, 29). Fasting becomes a risky venture without cortisol: patients with untreated adrenal insufficiency weaken profoundly, collapse, and are liable to die in hypoglycemia if they attempt a prolonged fast.

The danger of hypoglycemia in patients with adrenal insufficiency is compounded because the suggestive sweating, pallor, and tachycardia may be missing. As in many patients with chronic fasting hypoglycemia, neuroglycopenia—manifested by confusion, personality changes, and psychotic behavior—usually predominates. Proper medical evaluation may therefore be postponed. Apparently nonspecific symptoms such as sluggishness and irritability (which were noted in our patient) are common in adrenal insufficiency; because they are often accompanied by low-normal blood sugars and alleviated by frequent meals, they may be early portents of serious hypoglycemia.

Hypothermia or fever can be important diagnostic or prognostic clues.^{12,22} Hypothermia is a well-known concomitant of hypoglycemia. Originally noted during severe hypoglycemic reactions, it has also been found in otherwise unsuspected, sporadic episodes. In milder hypoglycemia cases, hypothermia may be caused by a combination of increased heat dissipation by the skin and decreased caloric production. In patients with hypoglycemic coma, hypothermia has been presumed to be due to hypothalamic dysfunction.¹² Fever, found in our patient, is an unusual manifestation of hypoglycemia possibly resulting from “stimulation of the hypothalamo-sympathetic regulated mechanisms of heat production.”²² The presence of fever is important for two reasons. First, when combined with neurologic abnormalities characteristically seen in hypoglycemia (such as hypertonia, hyperreflexia, and cortical depression), it may simulate cerebral hemorrhage, meningitis, or septic cavernous sinus

thrombosis—thus misleading the unwary physician. Second, when fever is present restoration of full consciousness lags behind restoration of the blood glucose level. (It took 3 days for our patient's confusion and irritability to clear, although his fever had disappeared on the first day with return of his blood sugar to low-normal levels.) In cases of prolonged hypoglycemia, fever may be an important sign of increased intracranial pressure and cerebral edema, and intravenous mannitol therapy may be life-saving.

TUMOR HYPOGLYCEMIA

Case 4. Adrenocortical Carcinoma

A. F., a 51 year old woman, was well until a year before her admission to the Long Island Jewish Medical Center in March 1970 for hypercorticism. Evaluation (Table 4) revealed elevated urinary 17-hydroxysteroids and 17-ketosteroids which were not suppressible with dexamethasone. A right suprarenal mass was clearly visible on intravenous pyelography. At operation a right adrenal carcinoma weighing 850 gm. was removed. Postoperatively the patient demonstrated clinical and chemical improvement (Table 4).

In June 1971 a chest x-ray revealed bilateral lung metastases, and elevated levels of urinary steroids recurred; o,p'-DDD therapy was started but soon stopped because it induced severe nausea and vomiting. In March 1972 streptozotocin was started, but the patient continued to show progression of her metastatic disease, and experienced daily drenching sweats and palpitations in the morning before breakfast. She was hospitalized in August 1972, and while hospitalized had a generalized seizure one morning before breakfast. Blood sugar drawn right after the seizure was 15 mg. per 100 ml. The patient was treated with frequent feedings and was discharged. She was admitted to Queens Hospital Center 2 days later with mental confusion. Blood sugar on admission was 30 mg. per 100 ml. The patient was treated with intravenous glucose. Blood sugar responses (mg. per 100 ml.) to glucagon stimulation (1 mg. intramuscularly) were: 44 fasting, 54 at 5 minutes, and 79 at 15 minutes. The patient was discharged only to be re-admitted unconscious 24 hours later with a blood sugar of 20 mg. per 100 ml. She died later that day.

On postmortem examination there were metastases to the liver and both lungs. The pancreas was normal.

Table 4. Urinary Corticosteroid Excretion in a Woman with Adrenocortical Carcinoma

	17-KETOSTEROIDS (normal = 4-15 mg./24 hr.)	17-HYDROXYSTERIODS (normal = 2-9 mg./24 hr.)
<i>Before surgery</i>		
Baseline	107	16
8 mg. dexamethasone	109	20.8
Metopirone test	57.7	11
<i>After surgery</i>		
3 Weeks	4.48	3.97
6 Months	6.3	3.0
15 Months (metastatic carcinoma)	91.0	17.5

Hypoglycemia associated with adrenocortical carcinoma, first reported by Anderson in 1930, is a rare and poorly understood syndrome. Of the 14 reported cases of "Anderson's syndrome," 5 patients had associated hypercorticism, 4 were virilized, and 5 had only hypoglycemia as the major clinical abnormalities.¹⁵ It is paradoxical that adrenocortical carcinoma should produce hypoglycemia in the presence of excess cortisol, a diabetogenic hormone (see Table 1). This paradox remains unresolved.

Adrenocortical carcinoma is one of many extrapancreatic tumors capable of producing clinically apparent hypoglycemia. Over 200 cases of extrapancreatic tumors causing hypoglycemia have been reported. These tumors can be logically classified by their embryologic cell origin¹⁰ as shown in Table 5.

Why is hypoglycemia associated with these tumors? Various theories have been proposed, but an adequate explanation remains elusive. The suggested mechanisms have included secretion of insulin-like substances, excessive glucose utilization by the tumors, tumor production of nonhormonal hypoglycemic substances, and massive metastatic replacement of the liver.^{4, 14, 23, 29} Though convincing experimental evidence is lacking, there is presently some enthusiasm for the idea that these tumors produce nonhormonal metabolites that cause hypoglycemia. The leading candidates are tryptophan and its metabolites, which have been reported in high concentrations in tumor tissue.²⁷ These compounds may potentiate the action of endogenous insulin by inhibiting hepatic gluconeogenesis, most likely at the level of phosphoenol-pyruvate formation from oxalacetate (Fig. 2, reaction 16).

Extensive liver metastases can produce hypoglycemia by preventing hepatic glycogen formation and storage. This mechanism can be tested clinically by glucagon administration, which increases blood glucose via hepatic glycogenolysis. In our patient, as in most with tumor hypoglycemia, the normal response to glucagon indicated that glycogen stores were

Table 5. *Common Causes of Tumor Hypoglycemia*

I. Mesodermal
A. Mesenchymal (most common)
1. Spindle cell fibrosarcoma (most common of this group)
2. Benign fibroma
3. Leiomyosarcoma
4. Mesothelioma
5. Rhabdomyosarcoma
6. Liposarcoma
7. Reticulum Cell Sarcoma
B. Adrenocortical carcinoma
II. Endodermal
A. Hepatoma
B. Cholangiocarcinoma
C. Gastric carcinoma
D. Carcinoma of the cecum
E. Wilms' tumor

not depleted, and that other mechanisms were responsible for the hypoglycemia.

Therapy for extrapancreatic tumors causing hypoglycemia includes surgery, radiation, drugs, or a combination of these.

Excision of these tumors can lead to remission for prolonged periods in some of the slow-growing tumors (e.g., mesotheliomas). Patients with adrenal carcinoma usually do poorly because of fast growth of this tumor;²⁵ 5 year survival rates are less than 10 per cent in most series.

o,p'-DDD may be useful in treating adrenocortical carcinoma, with or without hypoglycemia. With its selective adrenolytic effect against both tumor tissue and its secretory activity, this drug can cause tumor regression and thereby alleviate the hypoglycemia. o,p'-DDD is administered in maintenance dose of 1 to 10 gm. daily given orally in divided doses. Toxicity includes nausea, vomiting, diarrhea, apathy, and psychotic depression. These last two symptoms have been major deterrents to use of the drug.¹¹

Streptozotocin, a nitrosourea compound isolated from *Streptomyces achromogenes*, is useful in some cases of islet cell carcinoma;²¹ the drug destroys beta cells and thereby reduces plasma insulin levels. It is usually given as a single intravenous injection once a week. Use of streptozotocin to treat extrapancreatic tumors is experimental. It is interesting to note that our patient's symptoms of hypoglycemia actually began while she was on streptozotocin, as experimental chemotherapy for lung metastasis. The reason for this is unknown to us.

Diazoxide, by decreasing insulin secretion, has been found useful in treating some cases of insulinoma. It has been tried without effect on a few patients with extrapancreatic tumors.

No definite treatment now exists for hypoglycemia associated with extrapancreatic tumors. Until alternatives are available the various palliative measures we have described may be tried.

ALCOHOL-INDUCED HYPOGLYCEMIA

Case 5. Alcohol and Insulin

W. N., a 42 year old alcoholic also suffering from diabetes mellitus (on 20 units NPH insulin daily), was admitted to the emergency room of the Queens Hospital Center following a grand mal seizure several hours after an alcoholic binge. The patient was unconscious and had a blood sugar of 17 mg. per 100 ml. He regained consciousness momentarily after injection of 50 per cent glucose, but suffered a second convulsion and was admitted to the intensive care unit where he was intubated and placed on assisted ventilation.

On examination the patient was having myoclonic seizures and decorticate movements of the extremities. Deep tendon reflexes were unobtainable and the Babinski sign was present bilaterally. The pupils were dilated and equal with sluggish reaction to light. The spinal fluid examination, including glucose, was normal. Blood gas analyses revealed a severe metabolic acidosis with compensatory respiratory alkalosis. The acidosis improved after administration of sodium bicarbonate.

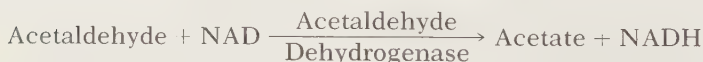
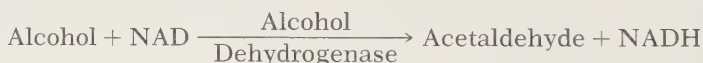
In spite of a 10 per cent glucose infusion and intermittent injections of 50 per cent dextrose and cortisol, the patient's blood sugar was 45 mg. per 100 ml. 6 hours after admission and 33 mg. per 100 ml. 9 hours after admission. Blood sugars over 90 mg. per 100 ml. were reported 16 hours after admission.

Despite correction of the hypoglycemia, the patient remained comatose. The day after admission he was hypoxicemic and gradually developed the clinical and radiologic picture of wet lung ("adult respiratory distress") syndrome, requiring continuous administration of 50 to 100 per cent oxygen through an Engström ventilator. After the first day his temperature fluctuated between 101 and 103° F. without any response to cephalothin and gentamicin. White blood cell counts remained normal. Blood, urine, and sputum cultures were negative. He died on the ninth day of hospitalization.

Autopsy examination of the brain revealed laminar necrosis of the cerebral cortex and focal necrosis in the basal ganglia, compatible with severe hypoglycemia and/or anoxia. Histologic examination of the lungs was compatible with the adult respiratory distress syndrome.

In this case, severe hypoglycemia followed concomitant use of alcohol and insulin. The fatal outcome is not unusual. In adults, hypoglycemia produced by this combination of drugs is the most common cause of death associated with drug-induced hypoglycemia.^{1, 26} Nor is the association of hypoglycemia with alcohol ingestion merely coincidental. In adults between 30 and 60 years of age, alcohol (alone or combined with insulin) accounts for 70 per cent of all cases of drug-induced hypoglycemic coma.²⁶ How, then, does alcohol cause hypoglycemia? The mechanism, elucidated during the last decade,^{6-9, 16, 24} is inhibition of hepatic gluconeogenesis during fasting, when hepatic glycogen stores are already depleted. Such glycogen depletion, found in many chronically malnourished alcoholics, can also be produced experimentally in normal subjects by a 2 to 3 day fast.

This inhibition of hepatic gluconeogenesis is linked with increased consumption of the hydrogen acceptor nicotinamide adenine dinucleotide (NAD)* during alcohol metabolism, resulting in accumulation of its reduced form, NADH (Fig. 2, reactions 23, 24**).



Though some NADH can be reoxidized in the gluconeogenic pathway (reaction 11), when the amount involved is very large lactic acidosis may result (reaction 22):



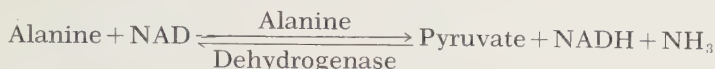
Most important for glucose homeostasis, this reaction reduces the amount of pyruvate available to be converted, via oxalacetate, to phosphoenol-pyruvate (reactions 15-16). This intramitochondrial conversion of pyruvate is a key metabolic step in gluconeogenesis.

Alcohol metabolism, by decreasing the intra-hepatic NAD/NADH ratio, suppresses other NAD-dependent enzymatic steps required for gluconeogenesis during fasting. These steps include:

*In earlier terminology, NAD was known as diphospho-pyridine nucleotide (DPN).

**All reactions noted in this section refer to those in Figure 2.

(1) The extramitochondrial oxidative deamination of alanine to pyruvate (reaction 25—probably more important in the kidney than in the liver):

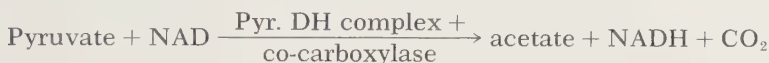


In the liver, the alanine-pyruvate cycle—the most important supplier of pyruvate—operates mainly through transamination (reaction 26 and Fig. 3); serine, cysteine, cystine, and glycine provide pyruvate through complex non-oxidative deamination (reaction 29).

(2) The extramitochondrial oxidative deamination of glutamine, supplying alpha-ketoglutarate into the Krebs cycle (reaction 27). The rest of the glucogenic amino acids enter gluconeogenesis through mechanisms that are not NAD-dependent (reactions 26, 29).

(3) Three intramitochondrial reactions operating in the Krebs cycle involving transformation of isocitrate, alpha-ketoglutarate, and malate (reactions 19, 20, 21).

(4) The oxidative decarboxylation of pyruvate by the pyruvic dehydrogenase complex (reaction 17):



It is obvious that suppression of the reactions shown in (2), (3), and (4) dampens Krebs cycle activity, thus decreasing oxalacetate formation and retarding gluconeogenesis.

(5) Entrance of glycerol into the gluconeogenic pathway. Glycerol, a product of triglyceride hydrolysis in adipose tissue, is phosphorylated in the liver, and the glycerophosphate so produced is incorporated into the gluconeogenic pathway by dehydrogenation with eventual formation of fructose-1-6-diphosphate (reactions 10, 9, 8a, 8).

Other metabolic steps suppressed by the decreased NAD/NADH ratio associated with alcohol metabolism include: conversion of galactose into glucose (reaction 3b), the direct oxidative pentose pathway (reaction 4a), and oxidation of fatty acids (reaction 28). It is apparent that the combined accumulation of glycerol and fatty acids may play a role in the fatty changes generally observed in the alcoholic liver.

To summarize, in addition to its suppression of the glycerol-glyceraldehyde pathway, alcohol suppresses the gluconeogenic production of pyruvate and oxalacetate from the glucose precursors lactate and amino acids. This results in decreased production and release of glucose from the liver during fasting. There is experimental evidence that non-NAD-dependent precursors of glucose like fructose¹⁶ and pyruvate,⁷ and even the redox dye methylene blue,¹⁷ which is capable of oxidizing NADH, can rapidly restore hepatic glucose output to normal.

Alcohol-induced hypoglycemia is less frequent than the widespread abuse of alcohol would suggest. Some cases may therefore be attributable to individual susceptibility caused by congenital or acquired enzymatic

abnormalities.¹⁵ This seems likely in alcoholic subjects in whom hypoglycemia has occurred in the presence of moderate blood alcohol levels, without alcoholic stupor or coma. There is also marked vulnerability to hypoglycemic effects of alcohol in patients with poor ability to activate gluconeogenesis during fasting, as in adrenal insufficiency; and in patients with accelerated return from the post-prandial metabolism of carbohydrate and protein to the starvation metabolism of fat, as in thyrotoxicosis and poorly controlled diabetes.

In experiments performed on fasted dogs with chronic end-to-side portacaval shunts, Lochner et al.¹⁶ showed that alcohol produced both a prompt 65 per cent fall in mean hepatic glucose output (favoring hypoglycemia) and 25 per cent inhibition of peripheral glucose utilization (favoring hyperglycemia). Hypoglycemia occurred only when the magnitude of decrease in hepatic glucose output exceeded the magnitude of inhibition of peripheral glucose utilization. Exogenous insulin certainly aggravates alcohol-induced hypoglycemia: it stimulates peripheral utilization of glucose and decreases hepatic glucose output (Table 1). Hypoglycemia induced by alcohol and insulin, as in our patient, may be so refractory that it produces irreversible cerebral damage resulting in prolonged coma, mental retardation, idiocy, or death. Recovery depends entirely on early recognition and treatment of the hypoglycemic state; 50 per cent glucose, given by rapid intravenous injection hourly or half-hourly as indicated by Dextrostix determinations of blood glucose, is the brain-sparing and life-saving medication. In addition, an intravenous drip of 10 per cent glucose should be maintained until alcohol is completely eliminated, NAD stores repleted, and hyperglycemia established. The therapeutic goal is to establish and maintain hyperglycemia for as long as necessary. Glucagon cannot be expected to have an immediate effect on this type of hypoglycemia because hepatic glycogen stores are depleted in malnourished alcoholic individuals. Yet the direct (but slower) action of glucagon on gluconeogenesis, in combination with adrenal glucocorticoids, may help maintain hyperglycemia.

Simultaneous supplementation of electrolytes and bicarbonate is needed to correct electrolyte imbalance and lactic acidosis. Administration of B-complex vitamins is usually necessary because most heavy drinkers are vitamin-deficient, and because increased consumption of co-factors by the rising metabolism of carbohydrates could precipitate acute avitaminosis.

DRUG-INDUCED HYPOGLYCEMIA

Case 6. Sulfonylurea Overdose

E. I., a 74 year old man, was admitted to the emergency room of Queens Hospital Center drowsy, sweaty, unable to speak, and behaving bizarrely. A blood sugar, immediately obtained was reported as 60 mg. per 100 ml.; cerebrospinal fluid sugar was 30 mg. per 100 ml. The patient responded rapidly and dramatically to 100 ml. of 50 per cent glucose given by mouth. He then revealed that one day earlier he had been told by his physician that his blood sugar was "over 200," and was started on a loading dose of 6 tablets of tolbutamide (Orinase) in 3 equally divided doses.

A sharp drop in blood sugar concentration to low normal levels can cause symptoms and signs of hypoglycemia, as this patient's case illustrates. This is especially true in older diabetics with cerebrovascular atherosclerosis. For this reason a loading dose of oral hypoglycemics is no longer recommended for initiating treatment.

The sulfonylureas lower blood sugar primarily by stimulating secretion of insulin from the beta cells. The incidence and severity of the hypoglycemia provoked by this mechanism is greater with the long-acting chlorpropamide (Diabinese) than with the other sulfonylureas. In view of its total excretion by the kidneys, chlorpropamide is contraindicated even in mild renal failure; the other sulfonylureas, metabolized in the liver, are contraindicated in hepatic failure. Because the metabolic product of acetohexamide (Dymelor), hydroxyhexamide, is even more active than the oral agent itself and is removed by renal excretion, it may accumulate and induce hypoglycemia in patients with renal failure. Of the oral hypoglycemic drugs the biguanide, phenformin, is least likely to decrease blood sugar to hypoglycemic levels. Combining two oral hypoglycemic agents may increase therapeutic efficacy but definitely increases the danger of hypoglycemia.

Other drugs potentiate the hypoglycemic effect of the sulfonylureas. These drugs include some of the antibacterial sulfonamides, the anti-inflammatory drug phenylbutazone, and the anticoagulant bishydroxycoumarin. The most commonly used anticoagulants, heparin and warfarin (Coumadin), apparently do not enhance the hypoglycemic activity of sulfonylureas.^{13, 26}

Particularly important for the severity of its hypoglycemia—mainly in young children—is acetylsalicylic acid. For almost a century it has been known that salicylates, in large doses, may have significant hypoglycemic effects in diabetic patients (probably more than in nondiabetics).²⁸ In children, the case fatality rate from salicylate hypoglycemia is higher (33 per cent) than from any other drug-induced hypoglycemia.²⁶

To *prevent* drug-induced hypoglycemias, physicians must recognize the most important underlying factors: restricted food intake (most common), abnormal hepatic or renal function, and adrenocortical deficiency. To *recognize* these hypoglycemias, physicians must consider the diagnosis in every unconscious patient, remembering that alcohol is the most common offender in patients between 30 and 60 years of age, and sulfonylureas the most common in patients over 60. To *treat* these hypoglycemias, physicians must start hypertonic glucose therapy early, add hyperglycemic hormones (cortisol and glucagon) when necessary, and continue therapy until drug effects have worn off and there is full recovery of the mechanisms that maintain glucose homeostasis. Only then can the patient return to a free and independent existence.

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Thyrotoxic Crisis and Myxedema Coma

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Endocrine diseases often take years to develop and are usually slowly progressive. In many instances hospital admissions are elective and diagnostic procedures may be comfortably scheduled in advance. Nevertheless, occasional emergencies arise in endocrinology. In this review we briefly consider the recognition and treatment of two of these life-threatening situations, thyrotoxic crisis and myxedema coma. Because these disorders are rare and often unrecognized, few physicians have the opportunity to develop adequate firsthand and clinical experience. Although much has been written about thyrotoxic crisis and myxedema coma, including several recent reviews,^{11, 12, 23, 24, 26} the treatment of each disorder remains difficult. Even in the best hands the mortality rates may be appreciable.

THYROTOXIC CRISIS

Thyrotoxic crisis, or thyroid storm, has been defined as a life-threatening augmentation of the manifestations of hyperthyroidism.^{16, 30} This condition has generally been observed in cases of extended duration and among untreated or partially treated individuals, rather than in newly diagnosed patients. Recent series^{15, 22} have shown that the incidence of thyrotoxic crisis is probably about 2 per cent of all admissions for hyperthyroidism. The true incidence of thyrotoxic crisis is not known, however, since physicians differ in the criteria which they will accept as diagnostic.

Classically, thyrotoxic crisis in the pre-drug era occurred shortly after operative treatment for hyperthyroidism. In such instances it probably

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was due mainly to the stress of surgery accompanied by manipulation of the gland, with sudden discharge of large amounts of thyroid hormone into the circulation. Improved preoperative preparation of the patient with sodium iodide, which reduces vascularity of the gland, and the thiourea derivatives, propylthiouracil and methimazole, which diminish the formation of hormone, has led to a decrease in the overall incidence of thyroid storm.^{15, 17, 30} At the present time most cases of crisis are associated with precipitating factors other than thyroid surgery.^{15, 22}

Infections of any kind are the most common precipitating cause of thyroid storm. Cardiovascular diseases, gastrointestinal disorders, emotional upsets, vigorous palpation of an untreated thyroid gland, toxemia of pregnancy, parturition, drug reactions, withdrawal from antithyroid therapy, radioiodine treatment for hyperthyroidism, surgical procedures of any kind, trauma, and diabetic ketoacidosis are all known causes of this syndrome.^{4, 15, 16, 17, 22, 30} Survival in reported series has generally ranged from 24 to 66 per cent,^{16, 17, 30} with an occasional author reporting greater than 90 per cent survival.^{1, 15} The mortality rate appears to have declined, largely as a result of the introduction of sodium iodide and antithyroid compounds. Further improvement in survival has been attributed to earlier recognition of the disorder, more intensive treatment of precipitating factors, and introduction of the antisympathetic agents. Despite these advances, mortality rates are still considerable.

The clinical features of thyrotoxic crisis are those of severe hyperthyroidism, with certain additional characteristic findings. Fever is almost universally present and may be high. Involvement of the central nervous system is prominent, ranging from coma or apathy to confusion, restlessness, agitation, and frank psychosis. Cardiac arrhythmias and tachycardia out of proportion to the fever are seen. Congestive heart failure is common, especially in older patients with underlying heart disease. The blood pressure is usually well maintained, but shock may be seen at a more advanced stage of the disease. Gastrointestinal manifestations include diarrhea, nausea, vomiting, abdominal pain, jaundice, mild hepatomegaly, and abnormal liver function tests. Physical findings may sometimes be suggestive of a surgical abdomen. The thyroid gland may be diffusely enlarged or nodular. One must remember that precipitating factors such as infection may produce fever, sweating, and tachycardia and thus mimic hyperthyroidism.

Since the outcome of thyrotoxic crisis is greatly influenced by the promptness of recognition and treatment, one must exercise a high index of suspicion. If thyrotoxic crisis is a strong possibility, treatment should be instituted immediately after drawing blood samples for hormone measurements.^{1, 11, 15, 24} The diagnosis of this condition must often be based on clinical grounds alone. The results of thyroid function tests are abnormal, but the range of values may overlap with those of patients with uncomplicated thyrotoxicosis.^{15, 22} It is worth remembering that a useful thyroid function test in an emergency situation is the two-hour uptake of radioactive iodine by the thyroid gland. If arrangements can be made to perform this test immediately, confirmation of the diagnosis of thyrotoxicosis can be made without unduly delaying the institution of proper ther-

apy. It is important to stress that one should not await complete laboratory confirmation of the diagnosis before beginning treatment.

The mechanism of this syndrome is unclear. One cannot easily ascribe it either to an abrupt increase of thyroid hormone production or to an inability of the patient to respond to the stress imposed by the thyrotoxic state.^{11, 24} The similarity between the manifestations of thyrotoxicosis and those of increased adrenergic activity has been noted for a long time. The use of antisympathetic agents in patients with thyrotoxic storm has given dramatic, even life-saving results.^{3, 4, 15, 21, 24} Decrease in tachycardia, tremor, lid lag, and fever has been noted. However, not all the clinical and laboratory manifestations of hyperthyroidism are completely normalized by the agents. Increased myocardial contractility and lipid abnormalities may be unchanged. Weight loss and increased oxygen consumption may be partially decreased or unchanged after the use of beta-blockers.^{7, 8, 13, 27, 31} Increased adrenergic activity, therefore, does not appear to be the sole mechanism of this syndrome.

Suggested treatment of thyrotoxic crisis includes the following:

ANTITHYROID DRUGS. Propylthiouracil (800 to 1200 mg. daily in divided doses) or methimazole (80 to 120 mg., in the same manner) by mouth or by nasogastric tube. Parenteral preparations are not currently available. These drugs will block new hormone synthesis in the thyroid gland but will not affect the release of stored hormone.

IODIDE. This drug directly inhibits thyroid hormone release. Lugol's solution, 30 drops by mouth daily in divided doses, or sodium iodide, 1 to 2 gm. intravenously every day, are generally used. It is recommended that iodide not be given until after the first large dose of antithyroid drug, in order to prevent the gland from utilizing the iodide as substrate for the synthesis of new hormone.

ANTISYMPATHETIC AGENTS. The commonly used agents are reserpine, which depletes catecholamines; guanethidine, which depletes catecholamines and also impairs their release; and propranolol and its congeners, which act as beta-adrenergic blocking agents. These drugs, as noted above, have a central place in therapy. Although all three have been used effectively, there are no controlled studies comparing these agents with one another. Reserpine was introduced for the treatment of thyrotoxic crisis more than a decade ago. Unlike guanethidine and propranolol, reserpine has a prominent central sedative effect which may be useful in agitated cases but may be undesirable when the patient is lethargic or mentally depressed. The drug generally must be given parenterally to be effective, the usual dose being 1 to 5 mg. intramuscularly every 4 hours for a total dose of 3 to 15 mg. in the first 24 hours. In one recent series of 8 cases the use of reserpine alone in these doses was associated with 100 per cent survival.⁴ It is noteworthy that even those patients with congestive heart failure improved when reserpine was given.

In at least one series guanethidine has given good results when used orally in doses of 1 to 2 mg. per kg. of body weight per 24 hours.¹⁵ When used in the recommended doses, both guanethidine and reserpine commonly produce orthostatic hypotension.

More recently, propranolol has been used in the treatment of thyro-

toxic crisis and has also given dramatic results.^{3, 21} This drug has a rapid onset of action and a short half-life. The usual dose is 1 to 5 mg. intravenously or 20 to 80 mg. orally every 4 hours. Propranolol has been known to precipitate cardiac failure, although some authors have stated that it may improve the cardiac efficiency of most thyrotoxic patients.³¹ Propranolol is contraindicated in patients with a history of asthma and should be used only with extreme caution in diabetics.

An antisympathetic agent must be used with care in a patient with overt or borderline congestive heart failure. In spite of these drawbacks, it is reasonable to employ one of these three valuable agents in the therapy of thyrotoxic crisis. We use either propranolol or reserpine, preferring the latter in patients with compromised cardiovascular status, asthma, or diabetes mellitus.

SEARCH FOR PRECIPITATING FACTORS. The diagnosis and treatment of any precipitating factor of thyrotoxic crisis is critical. Appropriate laboratory investigation should include: complete blood count, electrolytes, blood urea nitrogen, creatinine, liver function tests, chest x-ray, electrocardiogram, blood, urine, and throat cultures, and urinalysis. If an infection is suspected, appropriate antibiotics should be used after cultures have been obtained. We do not use antibiotics prophylactically. One should remember that thyrotoxic crisis may occur after the patient is admitted to the hospital for some other reason.

GENERAL SUPPORTIVE MEASURES. These include electrolyte and fluid therapy, antipyretics, cooling blankets, sponge baths, and sedatives such as the short-acting barbiturates. It is important to remember, as noted, that reserpine has a potent sedative effect.

ADRENAL CORTICOSTEROIDS. Although well-controlled studies of the use of high doses of corticosteroids (200 to 300 mg. of hydrocortisone or its equivalent intravenously) are lacking, these agents are usually recommended by most workers.^{11, 24, 28, 30} It seems reasonable to use corticosteroids in large doses initially because the biological half-life of cortisol is reduced in hyperthyroidism²⁰ and a state of relative adrenal insufficiency may occur.

Prompt and vigorous therapy is necessary to reduce the high mortality rate of unrecognized cases of thyrotoxic crisis. Improvement after treatment is generally seen within the first 24 hours. Doses of iodide and of antithyroid drugs should not be tapered too rapidly, since severely thyrotoxic patients may be prone to relapse. The antisympathetic agents should be maintained at lower doses as therapy continues. After the patient begins to improve, iodide should be withdrawn in preparation for the administration of ¹³¹I, often the treatment of choice. Antithyroid drugs should be given up to 2 or 3 days prior to the administration of ¹³¹I and resumed 2 days after.

Recently, plasmapheresis¹ and peritoneal dialysis⁹ have been used in patients with thyrotoxic storm. The patients had apparently received conventional treatment for crisis with little initial benefit. Both plasmapheresis and peritoneal dialysis were reported to remove significant quantities of thyroid hormone and to achieve clinical improvement. These new approaches to therapy require more extensive evaluation.

MYXEDEMA COMA

This condition has some features in common with thyroid storm: (1) it is rare, (2) it usually occurs in longstanding, severe cases, and (3) it is often precipitated by some intercurrent, stressful situation. Most patients with myxedema coma are elderly women, probably reflecting the age and sex distribution of hypothyroidism. Patients usually demonstrate the classical findings of myxedema: puffy face and extremities, dry, cold skin, loss of eyebrow and scalp hair, delayed relaxation phase of ankle jerk reflexes, and a large tongue. Additional features which may be seen in myxedema coma include a profound stupor, hypothermia with an absence of shivering, depressed respirations, and seizure activity. Most patients with myxedema coma have primary thyroid failure (i.e., post thyroiditis, post radioiodine, post surgery for hyperthyroidism, or idiopathic) but a small group of patients have hypothalamic or pituitary failure.^{4, 5, 10-16} In 77 cases reported up until 1961¹ the mortality rate was 66 per cent; in smaller series reported subsequently, where more vigorous therapy was given, the mortality rate ranged between 0 and 42 per cent.^{2, 10}

Hypothermia may be missed unless the clinical thermometer is well shaken down before use. Furthermore, since temperatures as low as 75° F. (24° C.) have been recorded, one must use a thermometer which records below the usual clinical temperature range. Rarely the patient may not exhibit hypothermia and may even be febrile, which should suggest an infectious process. Blood pressure may be extremely variable: the patient may be normotensive, slightly hypertensive, or even in shock. Sinus bradycardia may be routinely seen on the electrocardiogram, together with low voltage, diffuse T wave depression, and prolonged Q-T and P-R intervals. Cerebrospinal fluid pressure and protein concentration may be increased even in the absence of specific neurologic symptoms. Pericardial, pleural, and peritoneal effusions with high protein concentrations are not unusual; and hypercarbia, hypoxemia, and hyponatremia are commonly found. Hypoglycemia suggests hypothalamic-pituitary involvement,¹⁰ but some lowering of the blood glucose concentration may occur in primary thyroid disease alone.

In most cases of myxedema coma a precipitating factor can be found, and it may be difficult to determine whether thyroid deficiency *per se* has led to the entire clinical situation.^{18, 23, 25, 26, 29} A review of 76 cases reported up to 1961 revealed that the great majority lapsed into myxedema coma during the winter months, especially in cold localities where central heating was uncommon.³ It appears, therefore, that exposure to cold may help precipitate myxedema coma. Congestive heart failure, cerebrovascular accidents, infections, hypoxemia, hypercarbia, hyponatremia, hypoglycemia, sedative or anesthetic drug administration, trauma, and gastrointestinal bleeding have been implicated as precipitating factors.^{1-3, 10-25} Infections which develop in hypothyroid patients are treacherous and are extremely difficult to recognize. Typical responses to infection—fever, tachycardia, sweating, and leukocytosis—are often absent, confusing and delaying the diagnosis.

Many of the reported patients with this disease lapsed into severe stupor or coma only after they had been admitted to the hospital for another reason and developed an infection or another complication. Before lapsing into coma these patients sometimes did not look grossly myxedematous. This point is important because the partially treated or untreated hypothyroid patient should not be subjected to any procedure or drug which may precipitate myxedema coma. It must be remembered that these patients metabolize drugs more slowly than normal individuals and often have partially compromised respiration, leading to alveolar hypoventilation, hypercarbia, and hypoxia.^{14, 25, 26, 29} Hypoxia may also be due to congestive heart failure alone. In any event, hypercarbia and hypoventilation are of paramount importance in contributing to the patient's symptomatology. Hyponatremia may result from the inappropriate secretion of antidiuretic hormone,²⁶ leading to intravascular fluid expansion. The hyponatremia may aggravate the already depressed condition of the central nervous system and lead to seizures. Significantly, treatment of the convulsive disorder with barbiturates or other drugs may lead to further depression of the central nervous system.

As in thyroid storm, the diagnosis of myxedema coma should be primarily clinical. Here again one must exercise a high index of suspicion. The laboratory work-up should include: a chest x-ray, complete blood count, electrolytes, blood urea nitrogen, creatinine, blood glucose, urinalysis and appropriate cultures. The routine thyroid function tests should be drawn. There usually will not be enough time for a full scale evaluation to differentiate primary from secondary hypothyroidism. The serum level of thyroid-stimulating hormone (TSH) by radioimmunoassay is the definitive test. TSH levels are usually distinctly elevated in hypothyroidism associated with thyroid gland failure, with little or no overlap of the normal range. By contrast, in patients with secondary hypothyroidism (i.e., resulting from pituitary or hypothalamic disease), TSH levels are within or below the normal range.

Appropriate therapy for myxedema coma includes:

PROMPT TREATMENT OF PRECIPITATING FACTORS. Infection must be treated vigorously if suspected, remembering that hypothyroidism will mask many of the alerting symptoms.

GENERAL SUPPORTIVE MEASURES. (a) Ventilatory insufficiency may require intubation or tracheostomy. The latter is usually preferable because patients tend to relapse if mechanical ventilatory assistance is withdrawn too soon.^{5, 18, 23, 25, 26, 29} These procedures are not without hazard. In order not to depress the respiratory center further, hypoxia should be avoided and local anesthetics used only in small amounts.¹⁸ (b) The regulation of fluids and electrolytes is vital. If the serum sodium concentration is less than 115 to 120 mEq. per liter, small amounts of hypertonic saline may be used with monitoring of the central venous pressure line. Care should be taken not to compromise further an overburdened cardiovascular system. Usually there is pre-existing extracellular volume expansion with an impaired ability to excrete a water load.^{25, 26} (c) Hypoglycemia may be treated with concentrated glucose solutions, 25 gm. initially and more as needed. Intravenous fluids must be chosen to avoid worsening an existing hyponatremia.

THYROID HORMONE THERAPY. This consists of giving either triio-

dothyronine by nasogastric tube or thyroxine intravenously. Most authors feel that the previously recommended minute doses of thyroid hormone are ineffective in myxedema coma. Small doses were favored in the past because of the great sensitivity to thyroid hormone exhibited by myxedematous patients and the fear of precipitating cardiovascular problems. In the usual hypothyroid patient in whom stupor and coma are not present, it is probably best to begin with small doses of hormone; in emergency situations, by contrast, larger doses of exogenous hormone seem to improve survival considerably.^{2, 5, 6, 10, 18, 23, 26} Excellent results have been obtained with the use of 0.4 to 0.5 mg. of thyroxine given intravenously as a single dose, followed by 0.05 mg. intravenously or 0.1 mg. orally each day thereafter. Oral absorption of thyroid hormones may be uncertain at first and intramuscular absorption is variable.^{6, 18} Triiodothyronine has been used in doses of 12.5 μ g via nasogastric tube every 6 hours quite effectively.² The latter drug has been recommended in the past because of its more rapid onset of action, but the above doses of thyroxine have produced effects after the first 6 hours. Furthermore, at the present time parenteral preparations of thyroxine are readily available, whereas those of triiodothyronine are available only for investigational use.

A definitive choice of therapy is difficult to make at present, because there are no controlled studies comparing triiodothyronine and thyroxine. Some physicians favor the use of thyroxine because it is easier to administer, has a smoother effect, and probably has a lesser tendency to elicit arrhythmias. Intravenous administration of thyroxine avoids use of a nasogastric tube with its attendant hazard of pulmonary aspiration.^{6, 18, 23} Another consideration is that the effectiveness of treatment can be followed more easily with the routine thyroid function tests when thyroxine is used: The T_4 by column and T_3 resin uptake remain very low when triiodothyronine is employed. A cardiac monitor should be in place when either of these preparations is used since arrhythmias or other cardiac problems may develop.

ADRENAL CORTICOSTEROIDS. Hydrocortisone, 200 to 300 mg. intravenously, or its equivalent, should be given during the first day and quickly tapered. Most patients probably have normal pituitary-adrenal function, but sometimes it is difficult to rule out a pituitary disorder. Failure to treat adrenal insufficiency may be fatal and there is probably little risk from the acute use of steroids. At least one study¹² has shown that although the adrenal gland generally has normal responsiveness to ACTH in myxedema, ACTH release by the pituitary to some stimuli may be deficient.

REWARMING. Hypothermic patients probably should not be artificially rewarmed, except by blankets or by increasing the temperature of the room. Body temperature should return to normal with proper treatment. Elevating the body temperature abruptly may increase the oxygen requirement prematurely and worsen survival.^{6, 18, 23, 26, 29}

PRESSOR AGENTS. Drugs for the treatment of hypotension should be used only as a last resort. Not only may they be ineffective, but the combined administration of catecholamines and thyroid hormone may increase the incidence of arrhythmias.^{18, 23}

If the treatment of myxedema coma is successful, the patient will

have improved significantly by the end of the first day and will show considerable recovery in the first week.

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Barbiturate Poisoning — An Endemic Disease

Five Years' Experience in a Municipal Hospital

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Seventy years ago Fischer and Von Mering introduced diethyl barbituric acid (barbitone) as a hypnotic. The number of barbituric acid derivatives with hypnotic properties that were synthesized in the following years reached more than 2500. The easy availability of these drugs to the general public quickly resulted in their widespread use as an instrument of self-destruction. In more recent years the "drug culture" among young people with its addiction to "ups" and "downs" has added to the number of patients suffering from barbiturate intoxication.

In this report we review our experience in treating acute barbiturate intoxication, based in part on a retrospective study of patients admitted to Morrisania City Hospital for the 5 year period, 1967 to 1971. In this time, 126 patients fulfilling criteria for barbiturate intoxication were treated. Our experience re-emphasizes the importance of aggressive and meticulous supportive care, including the following: (1) maintenance of airway patency, (2) mechanical assistance to respiration when indicated, (3) measures to reduce the risk of pneumonia, (4) correction of hypotension, and (5) prevention of decubiti and other medical complications.

THE HOSPITAL STUDY

Patients and Methods

Morrisania City Hospital serves a largely economically deprived community with a population composed of approximately 183,000 whites and

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119,000 blacks; of this total, 25 to 40 per cent are Spanish-speaking. The median annual income of this population is \$4500 to \$8500.²⁷ The hospital has 330 beds; 110 are allocated to the medical service. There are approximately 3000 admissions to the medical service a year. In recent years admissions for barbiturate intoxication have been overshadowed by admissions for overdoses with other drugs, particularly heroin. (During a 17 month period which the present study overlaps, 149 patients were admitted with heroin intoxication.¹⁰)

Blood barbiturate levels in the 126 patients were determined by the colorimetric method of Baer.² By this method the barbiturate level is expressed in terms of secobarbital standard, with a correction factor provided for other barbiturates. When this factor is applied, the barbiturate level will always be higher than the secobarbital standard. For example, pentobarbital (Nembutal) and phenobarbital levels would be, respectively, 133 and 200 per cent of the reported barbiturate level. Common tranquilizers, sedatives, and antihistamines cause little or no interference by this method. Aspirin gives no reaction but, at toxic levels, salicylamide, dexchlorpheniramine, glutethimide, and methyprylone give weak reactions. Hydantoins, however, react strongly at therapeutic levels. A gas chromatographic method, now used at this hospital, was not used during the period of this study.

The patients were treated by house staff physicians under the supervision of attending physicians. House staff members varied in their application of possible modalities of therapy. Knowledge of the indications for endotracheal intubation and mechanical ventilatory assistance was evident on review of the charts and was well applied. Analeptic drugs were not employed in any patients.

A total of 158 patients were treated for barbiturate intoxication; 32 patients whose history was that of barbiturate ingestion but whose blood barbiturate level was negative were not included in the study. Thirty-six patients who were included, and who had elevated blood barbiturate levels, were known to have or were suspected of having taken alcohol or other sedative drugs concomitantly. The history given on admission was inadequate in many cases; frequently, family or friends knew the patient had ingested a sedative, but did not know its nature.

Because descriptions of states of unresponsiveness varied with examiners, and because there was some variation in description of the same patient by different examiners, the commonly used classification of Reed²³ was not used. Patients were arbitrarily divided into the groups described below. In about one third of cases the nature of the barbiturate was not determined. For this reason we have recorded the barbiturate level in terms of the secobarbital standard, though, as previously noted, the corrected barbiturate level, except for secobarbital, would be variably higher.

Clinical Findings

Sixty-one of the patients included in the study were in coma at time of admission. Blood barbiturate levels, expressed in terms of the secobarbital standard, ranged from 0.2 to 11.3 mg. per 100 ml.; in 20 patients

(32.8 per cent) the level was greater than 3 mg. per 100 ml. Sixty-five patients were not comatose and ranged in reactivity from deep stupor to drowsiness. Blood barbiturate levels, again expressed in terms of the secobarbital standard, ranged from 0.1 to 10.4 mg. per 100 ml.; in only 8 patients (12.3 per cent) was the level greater than 3 mg. per 100 ml. (Table 1).

Few patients were apneic or appeared to require respiratory assistance on admission, but endotracheal intubation and mechanical respiratory assistance were employed without hesitation in doubtful cases. A few patients were hypotensive. Three patients had cardiorespiratory arrests on arrival in the emergency room. One patient had ingested secobarbital and had a barbiturate level of 4.5 mg. per 100 ml.; another had ingested a barbiturate of unknown type and had a barbiturate level of 3.2 mg. per 100 ml. expressed as secobarbital. Both made uneventful recoveries. The third patient had ingested secobarbital and had a barbiturate level of 4.7 mg. per 100 ml.; she is one of the patients who had hemodialysis.

Table 1. *Blood Barbiturate Levels
(in Terms of Secobarbital Standard) in 126 Patients
with Barbiturate Overdose*

BARBITURATE LEVEL (mg./100 ml.)	NO.	PER CENT OF GROUP
<i>Comatose Patients (N = 61)</i>		
<1	20	32.8
1-2	14	23
2-3	7	11.5
3-4	4	6.6
4-5	5	8.2
5-6	4	6.6
6-7	3	4.9
7-8	1	1.6
8-9	1	1.6
9-10	1	1.6
10-11	0	0
11-12	1	1.6
<i>Noncomatose Patients (N = 65)</i>		
<1	35	53.8
1-2	12	18.5
2-3	10	15.4
3-4	2	3.1
4-5	3	4.6
5-6	1	1.5
6-7	0	0
7-8	0	0
8-9	0	0
9-10	0	0
10-11	1	1.5
11-12	0	0
> 12	1	1.5

Three patients were transferred to Montefiore Hospital and Medical Center, where they underwent hemodialysis. One was the patient mentioned above. A second patient was apneic and hypotensive on admission, and had a barbiturate level of 5.6 mg. per 100 ml.; she had ingested secobarbital and alcohol. The third patient had a barbiturate level of 8.5 mg. per 100 ml. (when corrected for phenobarbital, which he had taken, 17 mg. per 100 ml.) All three recovered.

There were 6 deaths. A 61 year old woman was admitted comatose, was awake 2 days later, but died suddenly on the seventeenth hospital day of a myocardial infarction. A 66 year old woman admitted in a stuporous state with a blood barbiturate level of 1.2 mg. per 100 ml. died on the third hospital day, apparently of pneumonia and overvigorous hydration in an attempt to induce diuresis; serum sodium was 111 mg. per 100 ml. and serum chloride was 82 mg. per 100 ml. on the day of death. An 82 year old man with a barbiturate level of 2.1 mg. per 100 ml. on admission survived initial coma, hypotension, and cardiac arrest (asystole), and was more alert on the fourth hospital day, but died on the twelfth hospital day of respiratory tract complications. A 74 year old man was admitted comatose with a barbiturate level of 4.6 mg. per 100 ml. and died comatose on the third hospital day with persistent, inadequately treated hypotension; peritoneal dialysis had been used. A 24 year old woman, admitted comatose and apneic with a blood barbiturate level of 6.7 mg. per 100 ml., died on the third hospital day of severe aspiration pneumonia; milk had been poured into her mouth prior to admission by a misguided friend (milk is believed by some members of our community to be an antidote to narcotic overdose). A 66 year old hypertensive woman, admitted comatose with a blood barbiturate level of 2.2 mg. per 100 ml. died 1 day after admission. She had bloody spinal fluid and barbiturate intoxication was probably not the cause of death. Two patients had cutaneous blisters compatible with barbiturate intoxication. Pulmonary edema complicated the initial course of two patients. Pneumonia developed in 8 patients and 2 additional patients had probable pneumonia.

Depression with suicidal gesture or intent was the most common cause for the ingestion of barbiturates in this series. However, a significant number of patients—particularly among the younger age group—had ingested barbiturates for “kicks.” The number of small children with accidental ingestion of barbiturates in this series was small (6).

The problem of the number of patients with significant depression of sensorium and paradoxically low blood barbiturate levels in this series is difficult to resolve with certainty. It is probable that many patients had ingested sedative medication of another type along with the barbiturate. Known or suspected histories of multiple simultaneous drug or alcohol ingestion was obtained in some patients, and the number of such cases is probably higher than the records indicate. Duberstein and Kaufman, in a study of heroin intoxication from this hospital, found that 38 per cent of patients admitted with a primary heroin overdose later gave a history of concomitant use of other drugs, e.g., alcohol or a sedative.¹⁰ We also have reservations about the accuracy of the barbiturate determinations in

some patients. The charts of a sizable number of comatose patients clearly indicated that a large amount of barbiturate was ingested, yet the barbiturate level was low. At the other extreme, a few patients without coma had blood barbiturate levels above those values given for the lethal dose in untreated patients (cited as more than 10 mg. per 100 ml. for long-acting barbiturates, more than 7 mg. per 100 ml. for intermediate-acting barbiturates, and more than 3 mg. per 100 ml. for short-acting barbiturates¹⁷). Many authors stress the variation in individual tolerance for barbiturates, especially in those who have taken barbiturates chronically for insomnia or epilepsy.

DISCUSSION

A common feature of the management of the patients in this series was an awareness of the need to maintain a patent airway and to provide mechanical respiratory assistance when indicated by the clinical state or blood gas analysis. Pneumonia and central respiratory depression are prominent causes of death in patients with barbiturate intoxication. Attention to adequate ventilation and respiratory tract care is of paramount importance.

Gastric lavage was used sporadically. Clemmensen and Nilson⁸ pointed out that until the middle of the 1940's the basis of treatment was massive gastric lavage, but that the amount of barbiturate which can be removed in this way is very small compared to the amount ingested. Moreover, aspiration pneumonia is a risk of this treatment. In the "Scandinavian method" reported by Clemmensen and Nilson, large scale gastric washouts are not used. If there is evidence that the drug was taken an hour previously or less, simple aspiration of gastric contents may be carried out. Matthew et al.²⁰ however, found that more than 200 mg. of barbiturate was recovered in 24 out of 65 patients who had gastric lavage within 4 hours of ingestion compared with only 1 of 65 patients lavaged after 4 hours. They recommended gastric aspiration and lavage in those patients who ingested the drug within 4 hours (unless it can be definitely established that fewer than 10 tablets or capsules were taken), or in unconscious patients for whom the time of ingestion is not known. They stressed that in the unconscious patient a cuffed endotracheal tube should be inserted prior to passage of the stomach tube, for protection of the lungs.

Forced diuresis using large volumes of intravenous fluids was attempted in some of the patients in this series, but its value cannot be analyzed. One of the deaths, as we noted, was probably related to the use of large amounts of fluids. With the exception of long-acting barbiturates such as phenobarbital, the major fraction of a barbiturate administered to man is presumably metabolized by microsomal enzymes in the liver.¹⁷ There have been reports^{15, 22} of decreased duration of coma following forced diuresis (and diuretic) combined with alkalinization of the urine (which increases diuresis and mobilizes barbiturate from cell to plasma) in intoxication produced by long-acting barbiturates. When the pK of the

barbiturate is within the physiologic range, alkalization results in ionization of the drug. Since cells, in general, are less permeable to the ionized form, reabsorption by renal tubular cells is decreased and urinary excretion is effectively increased. Unfortunately, only a few of the long-acting barbiturates, chiefly phenobarbital, have a pK in this range. Hadden et al.¹² point out, however, that no study has shown that forced diuresis significantly reduces the length of coma in patients intoxicated with short-acting barbiturates. They recommend that forced diuresis and alkalization be considered only in those patients who have taken long-acting barbiturates. Myschetsky and Lassen,²¹ in a review of their experience in the 10 year period since their introduction of this method, concluded that diuretic therapy is indicated only in the severest cases of intoxication with long-acting barbiturates, and is of secondary importance in management of severe barbiturate poisoning. Diuretic therapy is contraindicated in patients with gross impairment of cardiac or renal function.

Peritoneal dialysis was employed in two patients, and hemodialysis in three. Hemodialysis has been shown to be effective in decreasing duration of coma in poisoning by both long-acting and short-acting barbiturates,¹⁴ but Hadden et al.¹² have suggested reserving hemodialysis for patients with significant liver or kidney disease. The value of alkaline diuresis and peritoneal dialysis was studied by Bloomer,⁶ who concluded that they are of limited usefulness in the treatment of coma produced by short-acting barbiturates. Matthew¹⁸ indicated that at the Regional Poisoning Treatment Center, The Royal Infirmary, Edinburgh, Scotland, the results of peritoneal dialysis were disappointing, and he stopped using this procedure in barbiturate intoxication. Lee,¹⁶ in an extensive discussion of the role of peritoneal dialysis and hemodialysis, suggested that peritoneal dialysis had a very limited role to play in the management of acute barbiturate poisoning, but that hemodialysis did have a definite place in a few select cases. Examples he gave were those patients with renal insufficiency who had ingested long-acting barbiturates, and those with liver disease who had ingested short-acting or intermediate-acting barbiturates. Special indications for hemodialysis, unrelated to the serum levels but dictated entirely by the clinical state, will be found in the very young and the very old.

Hypotension complicated the course in a small number of patients in this series. Hypotension in barbiturate intoxication had been attributed to a number of factors in the past, but Shubin and Weil,²⁶ in their study of shock in barbiturate intoxication, found evidence that hypotension was not due to failure of arteriolar tone ("vasomotor collapse"). Rather, it was due either to absolute reduction in plasma volume or to relative hypovolemia in relation to an expanded vascular bed, with peripheral resistance usually normal or increased. The venous capacitance bed was implicated as the major site of pooling. While vasopressor agents increased blood pressure by increasing arteriolar constriction, cardiac output fell.

In a more recent discussion, Shubin and Weil²⁵ indicated that colloid solution is preferred for initial treatment of shock due to barbiturate intoxication. They advised infusion of up to 1 liter of 5 per cent albumin

solution as part of the initial treatment, with subsequent infusions of 1 liter of 10 per cent glucose alternating with 1 liter of 0.45 per cent saline in 5 per cent glucose. Careful monitoring of central venous pressure is necessary. They enjoined the routine use of vasoactive drugs for the treatment of hypotension due to barbiturate intoxication, because protracted use of these drugs leads to an egress of intravascular fluid in association with the increased capillary hydrostatic pressure. In this manner the hypovolemia, a major mechanism accounting for the initial shock, would be potentiated. They reserved use of vasoactive drugs in the temporary treatment of hypotension, while volume is being repleted, for the exceptional patient (citing as an example an elderly patient with severe coronary artery disease). Though renal failure was not a complication in any of our patients, it accounted for one sixth of the deaths at the Copenhagen center in the 1950's,⁸ presumably as a sequel to shock and prolonged hypoxia. Intact renal function is required for the elimination of the long-acting barbiturates.

Central analeptics were not used in our patients. This corresponds to current concepts in the management of barbiturate intoxication. Before the 1950's analeptic medication was used extensively. Reports^{9, 11} then appeared indicating that despite animal experiments to the contrary, analeptics did not increase the survival rate and may have increased the number of deaths from convulsions, vomiting, and cardiac arrhythmias. The marked decrease in mortality, from approximately 20 per cent in the 1940's to 1 to 2 per cent in later years at the Copenhagen center, is attributed to the introduction of antishock measures and other intensive supportive measures, as well as to the exclusion of the use of analeptic drugs.⁶

We noted pulmonary edema complicating the initial course of one patient. Setter et al.²⁴ reported that a clinical picture similar to pulmonary edema occasionally occurred in their patients without signs of heart failure, and was particularly common with short-acting barbiturates.

Bullous skin lesions were noted in 2 patients. Their presence has been reported in up to 6.5 per cent of patients suffering from acute barbiturate poisoning, and is believed to be sufficiently characteristic to strongly suggest the possibility of acute barbiturate poisoning in an unconscious patient.^{3, 4}

The electroencephalogram was not used to monitor our patients. However, it should be mentioned that while an isoelectric electroencephalogram is one of the criteria for a diagnosis of cerebral death,¹ a "flat" electroencephalogram is quite compatible with eventual clinical recovery from barbiturate poisoning.^{5, 13}

The overall mortality rate in this series was 4.7 per cent. Mortality rates in other recent series have been as low as 0.8 per cent.¹⁹

SUMMARY

Our experience over a 5 year period re-emphasizes the importance of the changed views of therapy in acute barbiturate intoxication which

have occurred as a result of Scandinavian experience,⁸ as modified by other workers in the field. The basis of treatment is aggressive, meticulous supportive care. Maintenance of airway patency, mechanical assistance to respiration (when indicated), measures to reduce the risk of pneumonia, correction of hypotension, and prevention of decubiti and other medical complications form the basis of treatment for most patients. Only in special circumstances are other measures employed. We agree with Hadden et al.¹² that well supported patients should not die from excessive barbiturate ingestion.

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Evaluation of Acute Chest Pain

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The evaluation of acute chest pain is perhaps the most frequent, most critical, and most challenging problem encountered by a physician. In a large municipal hospital patients often present to the emergency room or screening clinic with this complaint. However, acute chest pain may also be seen during a routine medical work-up, before or after operations, and during diagnostic procedures.

The primary aim of the physician should be to differentiate the more grave conditions, which carry the risk of sudden or rapid death, from the many less serious causes of chest pain.

Several general rules should be kept in mind when evaluating patients with this problem. First, there is little correlation between the severity of chest pain and the gravity of its cause. Second, there is poor correlation between the geography of the chest pain and its source. Last, a patient may have more than one disease process occurring simultaneously. The etiology of acute chest pain should not be immediately attributed to any observed abnormality until a definite cause and effect relationship can be established.

The evaluation of acute chest pain involves multiple skills on the part of the physician. He must be accomplished in history-taking, physical diagnosis, and interpreting diagnostic tests such as the x-ray film and electrocardiogram. The physician must be able to judge the patient's comprehension of his questions and his ability to respond. It should be remembered that patients occasionally are unable to give an adequate response to questions because of psychosis, sedation, senility, or language barriers.

CHEST PAIN OF MYOCARDIAL ORIGIN

Prompt recognition of chest pain associated with cardiac disease is important from both a diagnostic and a therapeutic point of view. Coro-

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nary artery disease is the most common etiologic factor. The various theories of pathophysiology of this pain have been reviewed by Gorlin.³ Chest pain resulting from coronary disease presents a spectrum of several entities, with angina pectoris at one end and myocardial infarction at the other. In between are several less well defined entities such as coronary insufficiency, status anginosus, preinfarction angina, and variant angina pectoris. An understanding of the differences will be helpful in formulating therapy.

The term angina pectoris was introduced by Heberden in 1768 and was intended to describe a sensation of strangling (angina) and anxiety. A more recent definition by Friedberg⁴ describes angina pectoris as a "clinical syndrome characterized by paroxysmal attacks of a distinctive pain or oppression, usually situated retrosternally, radiating commonly to the precordium and left upper extremity and occasionally to other adjacent areas, precipitated by effort or emotion and often also by other factors, and relieved rapidly by rest or nitrates." The precipitating events and the method of relief are the most important factors in the diagnosis of angina pectoris. Any pain which is characteristically brought on by exertion or cold and promptly relieved by rest or nitroglycerin should be considered angina pectoris.

While most physicians are familiar with the typical pattern of angina pectoris, it is the multiple exceptions that are of particular concern. Pain may be superficial or deep and located in almost any area of the chest. It may arise in or radiate to the neck, jaws, throat, cheeks, mastoid, shoulders, upper and/or lower arms, hands, and epigastrium. It should be remembered that pain in the more typical substernal region with radiation to the left arm is frequently encountered in patients with functional disease alone.

Typical angina pectoris induced by exertion is usually mild at the onset and becomes progressively more severe until the patient is forced to rest. However, Prinzmetal¹² described a form of variant angina pectoris in which pain characteristically develops at rest and, in fact, the patient can usually perform moderate exertion with no symptoms. Nocturnal angina pectoris is not associated with physical exercise but is thought to be related to the emotional excitement of dreaming, or to mild congestive heart failure. Unusual cases such as angina of micturition and angina with recumbency have been described.

Angina precipitated by exposure to cold is commonly seen. It is thought that a cold environment evokes an increase in peripheral resistance which then increases myocardial work and oxygen consumption. The effect of a highly humid environment should not be overlooked as another precipitating cause of angina.

Auscultation of the heart may help in the diagnosis of angina pectoris. An S4 gallop is frequently heard during an episode of pain and may disappear when the pain is relieved. The S4 gallop is not specific for coronary disease and only signifies a decrease in ventricular compliance. It is the transient nature of the gallop and its relation to the chest pain that may be helpful. Similarly, a transient murmur of mitral insufficiency associated with papillary muscle dysfunction has the same diagnostic sig-

nificance. Paradoxical splitting of the second sound has also been described during angina pectoris.

The response to nitroglycerin is important in the diagnosis of angina. In addition to relief of pain, the time necessary for this response is important. If relief comes 10 minutes or more after nitroglycerin is taken, it is probably not related to the nitroglycerin. The potency of nitroglycerin must also be considered, since a patient with angina may have a negative response to nitroglycerin if the tablets have decreased in potency. The patient's description of the typical flush sensation in his face and throbbing in the head helps assure that this has not occurred.

A simple maneuver may help confirm a diagnosis of angina pectoris. Levine⁸ describes carotid sinus massage producing sinus bradycardia as a mechanism for relieving angina. Pain secondary to abnormalities of the spine or gastrointestinal tract will not disappear. (The prompt relief of anginal pain with the Valsalva maneuver has also been noted, but this is no longer recommended because of the risk of sudden death.)

Between angina pectoris and myocardial infarction are the intermediary syndromes, acute coronary insufficiency, status anginosus, and preinfarction angina. The terms are not well defined and are used differently by various physicians.

Acute coronary insufficiency has been defined⁷ as prolonged coronary pain (usually more than 30 minutes) without enzyme or electrocardiographic evidence of myocardial infarction. The older term, status anginosus, has been replaced by preinfarction angina. This pain is similar to typical anginal pain but often occurs spontaneously, unrelated to emotion or exercise, and continues for varying periods of time without significant response to rest or nitrates. Crescendo angina refers to a pattern of angina pectoris which is increasing in both its frequency and severity. The importance in recognizing preinfarction and crescendo angina lies in the possibility of surgical (by-pass) or medical (anticoagulation) intervention before myocardial infarction occurs.

Electrocardiographic changes associated with these various manifestations of coronary artery disease are too numerous to describe in detail. ST segment depression is seen with typical angina pectoris while ST segment elevation is present with variant angina and myocardial infarction. It should be remembered that patients may have a normal electrocardiogram during angina and even during the early stages of acute myocardial infarction.

Other causes of myocardial pain include angina associated with ventricular hypertrophy. This is presumably caused by the myocardium outgrowing its vascular supply. This situation is commonly seen with aortic stenosis and aortic insufficiency. Anginal pain associated with right ventricular hypertrophy is thought to be due to similar pathophysiology involving the right ventricle. Unusual causes of myocardial pain include coronary embolism, Fabry's disease, carcinoid syndrome, the systolic click-systolic murmur syndrome, and use of certain drugs (ergot, pitressin, hydralazine, contraceptives).

It should be remembered that the incorrect diagnosis or suggestion of cardiac disease may lead to cardiac invalidism. This process, while not

life-threatening, may be incapacitating and is extremely difficult to reverse.

CHEST PAIN OF PERICARDIAL ORIGIN

The chest pain of pericarditis is often severe and sudden in onset. The pain is sharp, increases with inspiration and motion of the trunk, and may be relieved by bending forward. This type of pain may be due, in part, to associated pleurisy which is commonly present. Underlying this, there may be a dull prolonged pressure or ache which may be referred to the neck, arms, and back. This pain may be made worse by swallowing or coughing but is usually not affected by exercise. The most characteristic, but least common, is an intermittent pain which is associated with each heart beat.

Careful history may be helpful in determining the etiology of pericarditis. The very common idiopathic or viral pericarditis is usually preceded by an upper respiratory infection, while tuberculous pericarditis is preceded by a vague, several months long history of fatigue, fever, and weight loss. Post infarction or Dressler's syndrome³ is mostly related to a recent transmural myocardial infarction, although this event may not have been recognized clinically. Other etiologies such as uremia, lupus erythematosus, trauma, neoplasm, or radiation may also be suspected from the history.

The most characteristic finding on physical examination is the pericardial friction rub. This scratchy sound has three components—presystolic (atrial systole), systolic, and diastolic—any or all of which may be present. They are usually best heard at end-expiration, with the patient in a sitting position. The rub may decrease in intensity or disappear when the pericardial layers are separated by pericardial fluid. With pericarditis the chest pain and rub appear simultaneously, in contrast to acute myocardial infarction where a friction rub usually follows the onset of chest pain by several hours or days. Physical findings found with large pericardial effusion or constriction include Ewart's sign (a small area of dullness, bronchial breathing, and increased tactile fremitus near the angle of the left scapula, due to compression of the base of the left lung), inspiratory swelling of the cervical veins, and a paradoxical pulse.

The electrocardiogram in acute pericarditis usually shows ST segment elevation. This elevation is found in most leads with the exception of AVR and V1, which may show reciprocal depression. With acute pericarditis the amplitude and shape of the T wave is usually unchanged and the elevated ST segment is concave, while in acute myocardial infarction the T wave may be isoelectric or inverted and the ST segment is convex.

CHEST PAIN OF AORTIC ORIGIN

Prompt recognition of dissecting aortic aneurysm is important so that diagnostic procedures can be performed and a therapeutic regimen

formulated. A high index of suspicion is important in the diagnosis of aortic dissection. Any sudden, severe chest pain in a patient with hypertension, pregnancy, coarctation, blunt chest trauma, or any of the stigmata of Marfan's syndrome should suggest this diagnosis.

The pain is severe and usually sudden in onset. It reaches its peak intensity almost immediately, in contrast to the crescendo nature of the pain of myocardial infarction. Descriptive terms such as tearing or ripping are often used to describe this pain.

The varying location of pain may help determine the site of dissection. Pain starting anteriorly is generally seen with aneurysm of the ascending aorta, while pain starting in the back is seen with dissection beginning distal to the left subclavian artery.

Auscultation may reveal a murmur of aortic insufficiency if the aortic root is involved, or diminished heart sounds if pericardial tamponade has occurred. Inequality of the peripheral pulses may be appreciated: this indicates that major branches of the aorta have been compromised. Neurologic abnormalities may be seen when there is involvement of the intercostal arteries and ischemia of the spinal cord.

The electrocardiogram may be surprisingly normal. There may be evidence of left ventricular hypertrophy or myocardial ischemia. Rarely, the electrocardiogram may show a myocardial infarction when a coronary artery has been occluded by a dissecting hematoma.

Chest x-ray may be helpful in establishing the diagnosis. However, angiography is usually necessary to establish a definite diagnosis and to evaluate the extent of disease. The aorta may appear normal but more commonly the dissected portion is abnormally wide. The uninvolved portion may be tortuous or mildly dilated. If comparison x-rays are available, a recent change in aortic diameter strongly suggests the diagnosis. Irregular appearance of the aortic outline and abnormal separation of intimal calcification from the outer aortic margin (greater than 2.5 mm.) may also be seen. Left pleural effusion due to hemothorax may be present.

CHEST PAIN OF PULMONARY ORIGIN

Acute pulmonary embolism may be associated with two distinct types of chest pain. The more common is pleuritic pain, which may be associated with a pleural rub and occasionally chest wall tenderness. Less commonly, pain resembling typical myocardial ischemia may be present. This is usually found with a massive pulmonary embolus and is thought to be due to hypoxia and decreased coronary perfusion, or possibly mechanical distention of the wall of the pulmonary artery owing to pulmonary hypertension.

When pleuritic chest pain is accompanied by dyspnea, hemoptysis, anxiety, and cyanosis, the diagnosis is easily suspected. However, it should be stressed that this classic group of symptoms is commonly not present in patients with definite pulmonary embolism. In fact, pain may be a minor complaint, and wheezing may be a major finding.

Electrocardiographic abnormalities are present in approximately 70

per cent of patients with pulmonary embolus. These include: sinus tachycardia, S1 Q3 pattern, peaked P waves in leads II, III, and AVF, right axis deviation, T wave inversion V1 through V3, and right bundle branch block. Recently a leftward shift of the frontal plane axis has been found as a frequent manifestation of acute pulmonary embolus.⁹ The electrocardiographic changes are transient, usually lasting less than 36 hours, in contrast to changes of myocardial infarction, which are usually progressive and persistent.

The chest x-ray film may be normal, or may show signs of pulmonary embolism, pulmonary hypertension, or pulmonary infarction. Pulmonary embolism may cause increased segmental radiolucency with disappearance of vascular branches. Also seen are pleural effusions and evidence of decreased respiratory excursion of the diaphragm. Radiographic signs of pulmonary hypertension include dilated hilar arteries, dilated pulmonary artery trunk, evidence of right ventricular outflow stasis such as widening of the superior vena cava, and occasionally dilatation of the right ventricle and right atrium. The classical triangular shadow of pulmonary infarction is frequently not present and any pleural-based consolidation or plate-like atelectasis should be considered potentially as an infarction.

Although a multitude of laboratory tests are available, it is felt that a combination of lung isotope perfusion scan and arterial oxygen saturation is the most sensitive. If the lung scan and arterial Po_2 are normal, acute pulmonary embolism is unlikely.

Pneumothorax is characterized by the sudden onset of sharp chest pain with frequent radiation to the shoulder or back. It is usually made worse by deep inspiration and is associated with dyspnea and orthopnea. The diagnosis may be suspected by a history of chronic pulmonary disease or chest trauma and is easily proven by physical examination and chest x-ray. Pneumomediastinum, a complication of pneumothorax, is recognized by crepitations which may be palpated in the subcutaneous tissues of the neck and chest, or heard as a crunching sound (Hammand's sign).

Pleurisy, or inflammation of the pleurae, produces chest pain which is usually sharp, aggravated by inspiration, and frequently associated with cough and dyspnea. While pleurisy itself is usually easy to recognize, the underlying disease process may be difficult to identify.

CHEST PAIN OF GASTROINTESTINAL ORIGIN

Serious heart disease may be simulated by hiatus hernia or upper gastrointestinal abnormalities. In a series of 214 patients with hiatus hernia, Palmer¹¹ reported that approximately 5 per cent presented with pain resembling angina pectoris. Bennett and Atkinson¹ stated that 23 per cent of their patients admitted to the hospital with precordial pain were found to have gastrointestinal disease.

Hiatus hernia and reflux esophagitis are the most common gastrointestinal abnormalities simulating myocardial ischemia. The Mallory-

Weiss syndrome is occasionally seen in alcoholics and is recognized by the history of excessive vomiting, retching, and hematemesis. Precipitation of esophageal pain by exercise (especially straining or bending), or by emotion, was seen in 25 per cent of one series.¹ Esophageal pain was brought on by food more commonly than was cardiac pain. In addition, its burning character, relation to posture, and relief by antacid therapy usually point to the correct diagnosis. Perfusion tests are occasionally helpful in documenting the cause of pain in esophageal disease.

Biliary colic and cholecystitis may produce pain similar to that of myocardial infarction. It had been postulated that gall bladder disease was related to coronary disease and could precipitate angina pectoris, but more recent evidence appears to deny this relationship. Other abdominal problems such as achalasia, splenic flexure syndrome, peptic ulcer, and pancreatitis are usually readily diagnosed with the aid of simple x-ray films and laboratory procedures. Pancreatitis may be a particularly difficult diagnostic problem since it may cause electrocardiographic changes of myocardial injury.

CHEST PAIN OF MUSCULOSKELETAL ORIGIN

Chest wall syndromes are common causes of chest pain requiring differentiation from cardiac pain. Tietze's syndrome is a localized inflammatory disease of the upper central ribs or costal cartilages.⁶ The pain is usually gradual in onset and described as aching or gripping. It may be intensified with cough or deep inspiration. Examination reveals a firm fusiform swelling confined to one or more of the upper four costal cartilages. Heat and erythema are absent, while tenderness is usually present. Laboratory studies, including a complete blood count and sedimentation rate determination, are normal. The diagnosis is established by the clinical picture, the gradual response to moist heat and aspirin, and, if necessary, by biopsy, which reveals normal cartilage.

Chest pain is often the presenting symptom in patients with ankylosing spondylitis or cervical osteoarthritis. The anterior chest pain is thought to be secondary to nerve root compression or irritation of intercostal nerves and referral of pain anteriorly from involved vertebral joints. The pain associated with subacromial bursitis is associated with point tenderness and limitation of motion. The recognition of sensory deficits, motor weakness, and muscle atrophy helps establish the diagnosis of various thoracic outlet syndromes which also may be associated with chest pain.

A rare cause of chest pain is acute phlebitis of the superficial chest wall vein (Mondor's syndrome). Intercostal cramp is also rare and is similar to night cramp in the calves except for its location. Rib fractures, preherpetic as well as postherpetic neuralgia, and tumors of the rib or chest wall are other entities which must be excluded. Rib fracture must be carefully looked for in alcoholics; these patients frequently do not recall a history of trauma.

Extremely common is the precordial catch syndrome, which is re-

Table 1. *Causes of Chest Pain*

<i>Myocardial Origin</i>	<i>Pericardial Origin</i>
Coronary artery disease	Viral
Angina pectoris	Tuberculosis
Coronary insufficiency	Post-infarction (Dressler's)
Status anginosus	Uremia
Crescendo angina	Trauma
Pre-infarction angina	Neoplasm
Variant angina pectoris	Connective tissue disease
Myocardial infarction	
Aortic stenosis	
Aortic insufficiency	
Right ventricular hypertension	
Fabry's disease	
Carcinoid syndrome	
Systolic click-systolic murmur syndrome	
<i>Aortic Origin</i>	<i>Pulmonary Origin</i>
Dissecting aneurysm	Pulmonary embolism
Hypertension	Pneumothorax
Pregnancy	
Coarctation	Pneumomediastinum
Blunt trauma	
Marfan's syndrome	Pleurisy
	Pneumonia
	Abscess
	Connective tissue disease
<i>Gastrointestinal Origin</i>	<i>Musculoskeletal Origin</i>
Esophageal	Muscle
Hiatus hernia	Precordial catch syndrome
Esophagitis	Bornholm's disease
Mallory-Weiss syndrome	Intercostal cramp
Achalasia	
Peptic ulcer	Skeletal
Pancreatitis	Tietze's syndrome
Gall bladder	Osteoarthritis
Cholecystitis	Fractures
Biliary colic	Tumors
Splenic flexure syndrome	Bursitis
	Neurologic
	Herpetic neuralgia
	Radiculitis
	Thoracic outlet syndrome
	Vascular
	Mondor's syndrome
<i>Functional Origin</i>	
Neurocirculatory asthenia (anxiety neurosis)	
Factitious	
Malingering	
Addict	

lated to muscle spasm in the anterior chest wall. The very sharp, sticking, and localized pain is usually increased with inspiration and can be immediately abolished by a bending and stretching maneuver. Bornholm's disease ("devil's grip") is an epidemic myalgia which is caused by the Coxsackie virus. In addition to involvement of the pleura and diaphragm, there is frequent involvement of the muscles of the chest and shoulder. The diagnosis is usually established by being aware of its epidemic occurrence (although it may occur sporadically) and by noting diffuse muscle tenderness.

Although skeletal chest pain is most often benign, it must be remembered that it may coexist with angina pectoris. A study done by McElroy¹⁰ showed that skeletal pain was more common in patients with angina than in individuals of the same age with no heart disease. The mechanism is uncertain, though it is thought to be possibly reflex in nature.

CHEST PAIN OF FUNCTIONAL ORIGIN

Chest pain may be related to a vague functional syndrome originally described in 1871 by DaCosta and generally known as neurocirculatory asthenia.² Other terms such as irritable heart, effort syndrome, soldier's heart, and anxiety neurosis have also been used.

The patients usually complain of palpitations, nervousness, irritability, restlessness, and vague chest discomfort. Headache and dizziness are also described. Hyperventilation, sighing respirations, and fatigue are common features of this syndrome. Careful analysis usually reveals a general incapacity of the patient in adjusting to emotional or physical strain. Diagnosis essentially depends on being aware of the syndrome in addition to ruling out organic causes of chest pain.

Patients with factitious chest pain occasionally present to the emergency room of municipal hospitals. These patients, commonly addicted to narcotics, are seeking medication from unwary physicians.

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Non-Invasive Techniques in the Diagnosis and Management of Acute Cardiac Problems

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Direct recording of cardiac dynamics by cardiac catheterization techniques has been of great value in assessing cardiovascular function. However, these methods are complex, expensive, require highly trained personnel, and may result in significant morbidity and occasional mortality in seriously ill patients. In recent years, a number of non-invasive techniques for monitoring the cardiovascular system have been developed. These methods are safe, easily reproducible, and need less complex equipment for recording. Numerous studies have demonstrated a close correlation with direct measurements of the cardiovascular system. Non-invasive techniques are particularly effective for prolonged monitoring of patients.

This paper presents a summary of some new developments in this field and recent work done at our institution. The techniques that will be evaluated are those measuring: (1) systolic time intervals; (2) pulse wave transmission time: (a) Korotkoff sounds, (b) QF interval, which is the interval between the Q wave in the EKG and the femoral pulse; (3) continuous indirect arterial blood pressure recordings; and (4) premature beat arrhythmia monitor. The applicability of these techniques to the study of myocardial infarction, congestive heart failure, hyperthyroidism, and circadian rhythm of cardiovascular function will be reviewed.

TECHNIQUES

Measurement of Systolic Time Intervals

Systolic time intervals (STI) are obtained by simultaneous recordings of the electrocardiogram, the phonocardiogram, and the indirect carotid

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artery pulse tracing at the paper speed of 100 mm. per sec. (Fig. 1). The STI measured and studied include: total electromechanical systole (QS2), the left ventricular ejection time (LVET), the pre-ejection phase (PEP), and the ratio PEP/LVET (Weissler).¹⁷ The QS2 interval is measured from the onset of ventricular depolarization (onset of the Q wave in the EKG) to the first high frequency vibration of the aortic component of the second sound. The left ventricular ejection time is measured from the beginning of the upstroke of the carotid pulse to the trough of the incisural notch. The pre-ejection phase is obtained by subtracting the left ventricular ejection time from the QS2, and represents the interval from the beginning of the ventricular depolarization to the beginning of left ventricular ejection.

Weissler has calculated linear regression equations relating systolic time intervals to heart rate, and has obtained STI indices (QS2I, LVETI, and PEPI). These indices, which are rate-corrected systolic time intervals, can be used effectively to study and compare serial changes in cardiovascular function in patients.

Pulse Wave Arrival Time

Korotkoff sounds have long been utilized to measure arterial pressure indirectly. Rodbard¹² had studied simultaneously recorded Korotkoff sounds and the electrocardiogram, and measured the QKS and QKD, representing the time intervals between onset of electrical depolarization of the heart and the occurrence of the systolic and diastolic sounds in the brachial artery. These measurements are repeatable and easily obtainable. He has correlated the QKD interval with changing thyroid and cardiovascular function. In our laboratory a rate-corrected regression equation has been developed for the QKD interval (QKDI) which facilitates the study of serial changes in vascular dynamics. In addition, we have studied the pulse wave arrival time at the femoral artery (QF interval) by simultaneous recording of the EKG and an indirect femoral artery pulse tracing at a paper speed of 100 mm. per sec. The QF interval is the measure of time from the beginning of the Q wave in the EKG until the upstroke of the femoral artery tracing.

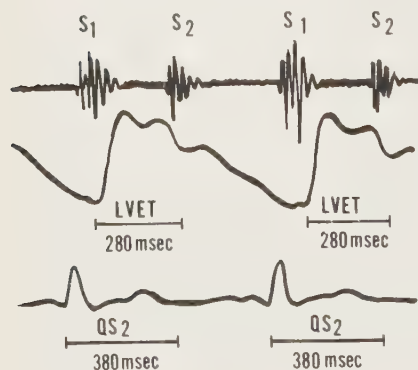


Figure 1. Measurement of systolic time intervals, using simultaneous recording of phonocardiogram, carotid artery tracing, and lead 2 electrocardiogram. QS₂ interval measures total duration of left ventricular systole from the onset of ventricular depolarization to the closure of aortic valve. LVET reflects events in the proximal aorta, measures the duration of left ventricular ejection. PEP (pre-ejection period) = QS₂ - LVET, represents the time interval from the beginning of ventricular depolarization until the opening of the aortic valve. PEP/LVET represents ratio of pre-ejection period to left ventricular ejection time.

Continuous Indirect Arterial Blood Pressure Recordings

Systolic and diastolic blood pressures can now be measured continuously every 2 to 15 minutes by a new Doppler ultrasound method.¹⁵ This method slightly underestimates systolic pressure and overestimates diastolic pressure when compared with direct intra-arterial pressure measurements; however, the consistency and reproducibility of this technique and the ease with which measurements can be performed and recorded through the 24 hour period make it exceedingly useful in the monitoring of acutely ill patients and in the management of patients with hypertension. The Doppler technique also allows the indirect recording of blood pressure in patients in shock, when Korotkoff sounds cannot be heard or recorded.

Premature Beat Arrhythmia Monitor

The ICR Arrhythmia Analyzer^{*} has been used intensively in our studies. This equipment offers the opportunity to quantify the premature beats occurring after myocardial infarction. Histograms performed at 30 minute intervals during the first 3 days after an acute myocardial insult provide an objective record of the number of VPC's, the time of the day when they occur, and the increase or decrease following appropriate therapy.

ACUTE MYOCARDIAL INFARCTION

The incidence of arrhythmias in patients with acute myocardial infarction is 95 per cent during the first 40 hours. Effective treatment of these arrhythmias with appropriate antiarrhythmic agents has significantly reduced the mortality associated with acute myocardial infarction. Quantification of ectopic rhythms provides a more reliable estimate of response to therapy than simple monitoring techniques. The premature beat arrhythmia monitor is an effective indicator of the frequency of ventricular premature beats (see Fig. 2).

Numerous investigators have attempted to correlate serial changes in the STI with hemodynamic alterations in patients with acute myocardial infarction.^{6, 9, 13} Because multiple hemodynamic variables affect the systolic intervals, discrepant results have been obtained in different studies. The marked increase in catecholamine release at the onset of acute myocardial infarction tends to shorten the QS2 and the PEP, while deteriorating myocardial function tends to prolong the PEP. The shortening of LVET with its close correlation to stroke volume appears to be the best indicator of directional change in following the course of acute myocardial infarction. Usually the LVET shortens during the first 6 days of acute myocardial injury with ensuing increase to normal within the next 3 weeks. Failure to do so appears to be a poor prognostic sign. Our studies,^{3, 5} corroborate these findings (see Table 1). Measurement of the QF interval has been exceedingly useful in our hands in evaluating pa-

^{*}Instruments for Cardiac Research, Inc., Syracuse, New York

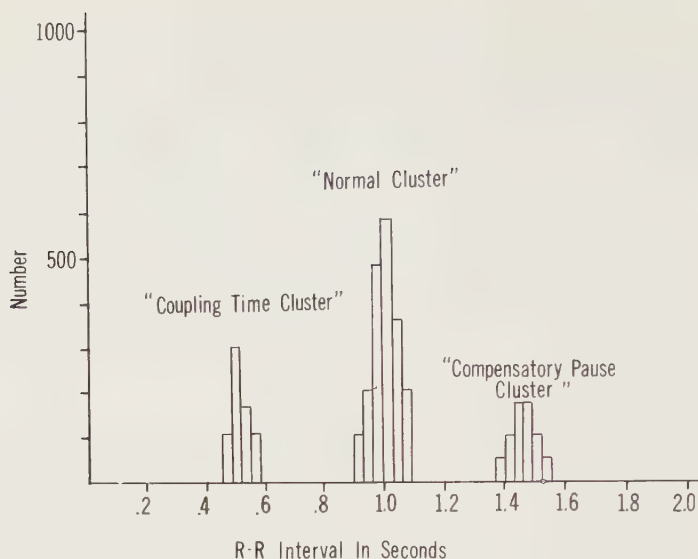


Figure 2. Histogram for isolated ectopic beats. Isolated ectopic beats form three clusters: (1) The R-R intervals between regular beats form the "normal cluster." (2) The short intervals between a regular beat and the following ectopic (premature) beat form the "coupling time cluster." (3) The long intervals between the ectopic beat and the following regular beat form the "compensatory pause cluster." (Courtesy of Instruments for Cardiac Research, Inc., Syracuse, New York.)

tients with acute myocardial injury. Our studies have shown a very close correlation between changes of LVET and QF intervals (see Table 1). As can be seen, mortality in patients with myocardial infarction was accompanied by progressive shortening of LVET with a concomitant prolongation of the QF interval. Patients who survived showed either minimal shortening or progressive lengthening of LVET with an unchanged QF interval.

CONGESTIVE HEART FAILURE

Patients with congestive heart failure have depressed myocardial contractility, decrease in the velocity and extent of myocardial fiber shortening, and depression of the maximal rate of rise of LV pressure (dp/dt), peak rate of flow from the ventricles, peak rate of change of flow velocity, and mean systolic ejection rate. The decreased rate of myocardial fiber shortening and of ejection are related primarily to a defect in contractility and secondarily to the greater tension or force required to eject blood from a dilated ventricle (Wallace).¹⁶ Patients in congestive heart failure have associated prolongation of the pre-ejection period and shortening of the left ventricular ejection time. These abnormalities revert toward normal with treatment and clearing of the heart failure.

Martin and colleagues⁷ have studied simultaneously externally meas-

Table 1. *LVETI and QF in Acute Myocardial Infarction
(Changes from Admission Baseline)*

PATIENT	AGE AND SEX	LVETI	QF	OUTCOME
M.O.	82 F	+60	-40	Recovery
M.G.	68 F	0	-10	Recovery
T.S.	36 M	-20	0	Recovery
B.N.	45 M	-10	+10	Recovery
M.R.	61 F	-23	+40	Expired
F.B.	72 F	-23	+40	Expired
W.B.	81 M	-25	+40	Expired
M.R.	55 M	-90	+60	Expired

ured systolic time intervals and internally measured indices of myocardial performance at rest, after exercise, and after acute interventions producing changes in contractility, preload, and afterload. Their findings demonstrate the extremely close correlation between external and internal ejection time ($r = 0.99$), and between pre-ejection period (PEP) and true isovolumic contraction time ($r = 0.94$). In addition, a close, inverse relationship was found between alterations in the rate of change in left ventricular pressure and pre-ejection period, with the pre-ejection period lengthening when the rate of left ventricular pressure change was decreased, and pre-ejection period shortening with an increase in the rate of left ventricular pressure change. Garrard and associates¹ correlated the PEP/LVET with the left ventricular ejection fraction and found a significantly close correlation ($r = -0.90$, $p < 0.01$).

Studies performed in our laboratory have confirmed the value of these indirect measurements in the diagnosis and management of congestive failure. Table 2 shows the results obtained in 20 normal subjects and 16 patients with documented untreated heart failure. With congestive heart failure there is significant prolongation of PEPI, shortening of the LVETI and concomitant prolongation of the interval from onset of electrical depolarization to brachial artery diastolic sounds (QKDI). In addition, the progress of the disease and response to therapy can easily be documented, as can be seen in Table 3, which shows studies

Table 2. *Systolic Time Interval and Pulse Wave Transmission
Time in Heart Failure*

	Q-S ₂ I ^o (msec)	PEPI (msec)	LVETI (msec)	PEP/LVET	Q-KDI (msec)
Normal	540±4	128±3	412±5	0.34±.02	244±3
Congestive heart failure	564±8	186±7	377±6	0.71±.06	335±7
p	<0.01	<0.001	<0.001	<0.001	<0.001

^oMean values ± Standard error of the mean

**Table 3. Serial Changes in Myocardial Function:
Alcoholic Cardiomyopathy**

PATIENT	DATE	HR (beats per min.)	LVETI (msec.)	PEPI (msec.)	PEP/LVET	EJECTION FRACTION (calculated)	(%)
E.J.	1/28/70	96	378	153	0.555	0.46	66
	8/11/70	88	350	195	0.800	0.12	17
S.W.	2/5/70	88	363	179	0.653	0.31	44
	7/24/70	100	374	184	0.706	0.24	34
M.P.	1/21/70	92	375	190	0.699	0.25	35
	6/29/70	82	389	193	0.640	0.325	47
	4/25/71	75	384	188	0.617	0.35	50
Normal Values*			413±10	128±6	0.345±0.04	0.70	100

*Mean ± 2 Standard deviations from the mean

in 3 patients with alcoholic cardiomyopathy in heart failure. Patients EJ and SW continued drinking heavily while on proper cardiac maintenance therapy, with evidence of further deterioration of myocardial function as shown by worsening of both PEP/LVET (increased) and ejection fraction (decreased). Patient MP stopped drinking and systolic time intervals show significant myocardial improvement.

The QKD intervals have been very useful in separating normal individuals from patients with congestive failure. As an index of myocardial contractility, arterial pulse wave timing is most helpful in the diagnosis of myocardial failure (see Table 2).

HYPERTHYROIDISM

An increase in heart rate, cardiac output, ventricular contractility, and oxygen consumption has been documented in hyperthyroidism. A decrease in all of these parameters occurs in hypothyroidism. Buccino² demonstrated an accelerated rate of muscle shortening and abbreviation of the time to peak tension in isolated papillary muscle preparation of hyperthyroid cats, and the opposite in hypothyroid muscles. Amidi and co-workers¹ have demonstrated in human subjects that the changes in ejection time (shortening in hyperthyroidism and lengthening in hypothyroidism) were indicative of increased and decreased myocardial contractility respectively.

The availability of non-invasive techniques has allowed the study of serial changes in cardiac function during therapy of hyperthyroidism and has permitted a better understanding of the effect of therapy. It has been of interest that pulse rate measurements, while reliably separating hyperthyroid from euthyroid or hypothyroid states, have not been helpful in discriminating euthyroid from hypothyroid states. Table 4 shows the results obtained studying 12 hyperthyroid patients treated with oral an-

Table 4. *Systolic Time Interval and Pulse Wave Arrival Time in Hyperthyroidism Before and During Therapy*

	HYPER	EU	HYPO	p1	p2
	(Mean Values $\pm$ 1 S.E.M.)				
Heart rate (beats/min.)	91 $\pm$ 4	78 $\pm$ 2	72 $\pm$ 3	0.01	NS
QS ₂ I (msec.)	523.4 $\pm$ 5	543.4 $\pm$ 4	554.4 $\pm$ 5	<0.01	NS
LVETI (msec.)	409.5 $\pm$ 4	404.8 $\pm$ 4	387.5 $\pm$ 4	NS	0.01
PEPI (msec.)	109.8 $\pm$ 2	134.4 $\pm$ 2	166.9 $\pm$ 8	<0.001	<0.001
PEP/LVET	0.278 $\pm$.01	0.375 $\pm$.01	0.507 $\pm$.03	<0.001	<0.001
QKDI (msec.)	233.2 $\pm$ 3	258.0 $\pm$ 6	297.9 $\pm$ 13	<0.001	<0.01

Hyper = Hyperthyroidism

Eu = Euthyroid

Hypo = Hypothyroidism

p1 = Represents the statistical significance of difference between Hyper and Eu values.

p2 = Represents the statistical significance of difference between Eu and Hypo values.

Hypo values were obtained in patients during transient phase of hypothyroidism while on therapy for hyperthyroidism.

tithyroid medication. Systolic time intervals and onset of depolarization to diastolic sound time (QKD) measurements were taken at 3 to 6 week intervals. During the transient hypothyroid state, there was a significant prolongation of the QKDI and PEPI intervals and marked increase in the PEP/LVET ratio. These abnormalities reverted towards normal with the return to the euthyroid state, as documented by clinical evaluations and thyroid function tests.

Rodbard¹¹ has shown that the arterial pressure wave timing clearly separates hyperthyroid, euthyroid, and hypothyroid patients. Our studies^{*} corroborate the great usefulness of this simple, innocuous technique (see Table 4).

The next table shows the typical serial changes in cardiac and thyroid parameters during treatment with propylthiouracil in an individual patient (Table 5).

CIRCADIAN RHYTHM

Circadian rhythm refers to the normal rhythmic variations of body function during the 24 hour cycle. Single or serial measurements of the cardiovascular system have usually not taken into account the effect of the phase of circadian rhythm on cardiac function. Similarly the usual therapeutic approach has disregarded these variations in myocardial function during the 24 hour cycle. Using the non-invasive techniques described (STI's and continuous indirect arterial pressure recordings), we have studied healthy individuals and patients with congestive heart failure during the 24 hour day at repeated 2 to 3 hour intervals and have been able to expand the studies performed by Reinberg¹⁰ and colleagues,

Table 5. *Cardiac and Thyroid Parameters During Treatment of Hyperthyroidism in a 50 Year Old Man (LW)*

	CARDIAC PARAMETERS					NORMAL VALUES
	0	60	80	100	120	
Time (days on therapy)	0	60	80	100	120	
Heart rate (beats/min)	100	77	71	81	83	
PEPI (msec.)	110	145	138	146	129	128±3
LVETI (msec.)	396	415	423	414	419	413±5
PEP/LVET	.311	.401	.361	.413	.345	.345±.02
Ejection fraction						0.70
QKDI (msec.)	217	284	271	266	248	244±3
THYROID PARAMETERS						
T ₃ Column μ /100 ml.	11.5	1.8	1.8		4.5	3-7
T ₄ Murphy/Pattee μ /100 ml.	23		3.8	4.2		5.5-15
TBI	0.75	1.20	1.20	1.0	1.00	1.10-0.90

and Schroeder¹⁴ and colleagues. Our initial studies¹⁸ involved 10 patients, age 18 to 48 years (mean age 28), with no evidence of cardiovascular disease studied for a 24 hour period. Heart rate, systolic and diastolic pressures (SAP and DAP), and STI's were recorded at 2 to 3 hour intervals. In 5 of the patients urine specimens were collected simultaneously at 2 to 3 hour intervals, and volume, creatinine, and catecholamine excretions were measured. Total urine catecholamines (free and conjugated) were eluted with boric acid solution and determined fluorometrically after oxidation to a trihydroxy-indole derivative.

The means of the change of the parameters of cardiovascular function (HR, SAP, DAP, STI) are presented in Table 6 as changes from the base line 9 A.M. determinations. The urinary findings represent mean absolute values of 2 to 3 hour collections. The results from the table clearly show important serial alterations in the parameters for the 24 hour period. During the 6 A.M. to 9 P.M. period there was a high level of catecholamine excretion, accompanied by significant shortening of the LVET and PEP, a slight increase in heart rate, and no significant blood pressure change. In contrast, during the 9 P.M. to 6 A.M. period there was a distinct reversal in the trend of all parameters, with a marked decrease in catecholamine excretion, a lengthening of LVET and PEP, a decreased heart rate, and a fall in systolic and diastolic pressure. The slowest heart rate, the lowest systolic and diastolic pressures, the most prolonged LVET and PEP, and the lowest urinary excretion of catecholamines occurred between 12 midnight and 6 A.M. (Table 7). Additional studies have been performed in 4 patients with congestive heart failure. Table 8 shows the range of maximal variation in both normal individuals and patients with heart failure. The patients with heart failure had blood concentrations of digoxin measured at 8 hour intervals within the therapeutic range. There were no significant differences in the blood digoxin levels during the 24 hour period of study.

Table 6. *Circadian Changes in Cardiac Parameters and Urinary Catecholamine Excretion*

Time (hour)	BASELINE (absolute values)*	CHANGE FROM BASELINE								
		9 A.M.	12 NOON	3 P.M.	6 P.M.	9 P.M.	12 MIDNIGHT	2 A.M.	4 A.M.	6 A.M.
Heart rate (beats per min.)	73.9 (4.1)	- 0.9	+ 3.1	+ 3.5	+ 2.7	+ 3.1	- 2.7	- 2.1	- 2.8	
Systolic arterial pressure (mm. Hg)	121.0 (3.0)	+ 2.5	- 0.5	+ 1.5	+ 0.5	6.0	- 6.0	- 5.0	- 10.0	
Diastolic arterial pressure (mm. Hg)	74.0 (1.8)	+ 3.0	- 0.5	+ 1.0	+ 2.0	+ 0.5	- 2.0	- 0.5	- 3.0	
QS ₁ I (msec.)	536.5 (5.9)	+ 3.6	- 11.5	- 15.9	- 0.5	+ 7.9	+ 6.7	+ 13.7	+ 10.1	
LVEFI (msec.)	413.4 (5.6)	+ 1.2	- 7.8	- 11.2	- 3.8	- 1.0	+ 0.7	+ 8.5	+ 0.8	
PEPI (msec.)	123.1 (5.7)	+ 2.4	- 3.7	- 4.7	+ 3.3	+ 8.9	+ 6.0	+ 5.2	+ 9.3	
Time (hour)	9-12	12-3	3-6	6-9	9-12	12-2	2-4	4-6	6-9	
Catecholamines ^c (μg)	77 (24)	112 (37)	96 (26)	119 (38)	35 (13)	45 (25)	28 (16)	35 (11)	108 (45)	

*Mean values ± Standard error of the Means

Table 7. *Maximal Circadian Changes of Cardiovascular Parameters in Normal Individuals (Means and Standard Error of the Means)*

		MAXIMAL		MINIMAL	P VALUE*
Heart rate (beats per min.)	6 P.M.	77±4	6 A.M.	71±3	0.02
Systolic arterial pressure (mm. Hg)	12 NOON	124±2	6 A.M.	111±2	<0.01
Diastolic arterial pressure (mm. Hg)	12 NOON	77±2	6 A.M.	71±2	<0.01
QS ₂ I (msec.)	4 A.M.	550±8	6 P.M.	521±6	<0.001
LVETI (msec.)	4 A.M.	422±6	6 P.M.	402±4	<0.01
PEPI (msec.)	6 A.M.	132±7	6 P.M.	118±6	0.02
Catecholamines (urine) (μg)	12-3 P.M.	112±37	2-4 A.M.	28±16	<0.05

*p values were obtained using Student's t-test for small sample sizes

These studies demonstrate a significant circadian rhythm of catecholamine excretion in normal men and in patients with heart failure with associated alterations in myocardial contractility, blood pressure, and heart rate. This suggests that the response to stress in the cardiovascular system in man will be significantly altered by the phase of the circadian rhythm.

SUMMARY

This article reviews some of the non-invasive techniques of value in the diagnosis and therapy of acute cardiac disorders. Systolic time intervals, pulse wave transmission time, continuous arterial pressure recording, and premature beat arrhythmia monitoring are defined and described. These methods appear to be useful and reliable in evaluating the course of acute myocardial infarction, congestive heart failure, and hyperthyroidism, and in studying the circadian rhythm of cardiovascular function.

Table 8. *Range of Maximal Variations (Means ± Standard Error of the Means)*

	NORMAL INDIVIDUALS	CONGESTIVE HEART FAILURE
Heart rate (beats per min.)	18±2	14±2
Systolic arterial pressure (mm. Hg)	20±2	21±3
Diastolic arterial pressure (mm. Hg)	13±2	13±1
QS ₂ I (msec.)	46±7	37±6
LVETI (msec.)	36±6	24±5
PEPI (msec.)	28±2	25±2

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Life-Threatening Arrhythmias

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Arrhythmias considered benign in a normal individual are potentially dangerous in a patient with a disabled heart.

In normal people, hemodynamic alterations occurring at heart rates of 40 to 160 per minute are physiologically compensated. Normal blood pressure and proper cardiac output are reestablished. The individual is not aware of his arrhythmia. If the heart is diseased, or other elements taking part in the oxygen transport system are disordered, a link in the compensatory mechanism is missing, and even a "benign" arrhythmia can produce a life-threatening situation. For example, a supraventricular tachyarrhythmia in a patient with severe mitral stenosis and congestive heart failure can cause serious complications requiring emergency treatment (Fig. 1).

As a basic principle, one should treat the patient who has an arrhythmia, and not the arrhythmia in itself. This requires careful clinical evaluation of the heart and coronary vessels, the musculocutaneous circulation (presence of cyanosis of the extremities, pallor, cold and clammy skin), the cerebral circulation (mental alterations), mesenteric circulation (signs of ischemia of the gastrointestinal tract), and the renal circulation (ischemia of the kidney).

Improved methods for early detection of life-threatening arrhythmias (monitoring devices, mobile and industrial Coronary Care Units, and intracardiac ECG), newer methods for treatment (including electrical defibrillators and electrical pacers), and to some degree newer drugs, have markedly improved the patient's chances for survival.

TACHYARRHYTHMIAS

Ventricular premature beats (VPB's) are frequently encountered in healthy young individuals (about 0.75 per cent) and in others under con-

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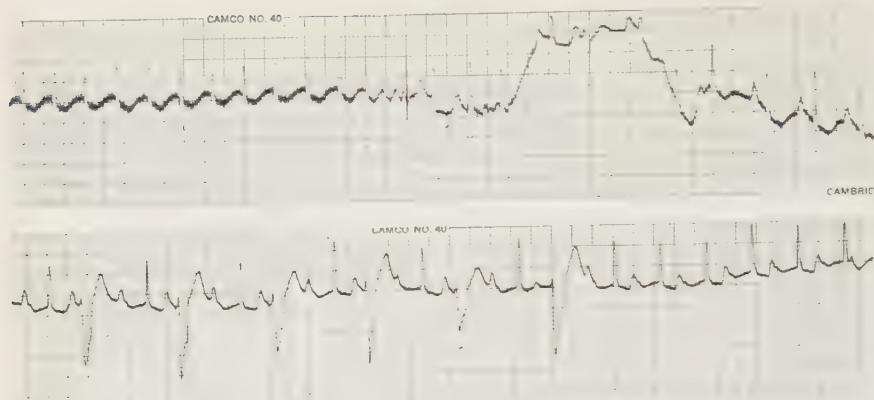


Figure 1. A 56 year old patient with severe mitral stenosis and heart failure was admitted to the coronary care unit in shock because of atrial flutter with 2/1 ventricular response resistant to digitalis and other drugs. Electrical conversion applied as a life-saving procedure broke the arrhythmia. A short run of ventricular extrasystoles (bigeminy), induced possibly by digitalis, is present after conversion.

ditions unrelated to a heart problem—after coffee, alcohol, tobacco, or sympathomimetic drugs; as a result of potassium and calcium depletion; or secondary to visceral reflexes or psychic and vagal stimuli. In the absence of clinical heart disease and in the presence of a normal EKG, VPB's appear to have little importance.

In patients with certain clinical features of myocardial infarction or angina and EKG abnormalities, VPB's have particular significance. Ventricular vulnerability is produced by inhomogeneous excitability of the diseased ventricle in its relative refractory period, and life-threatening arrhythmias may result. Ventricular tachycardia or ventricular fibrillation are more likely to be induced by early VPB's falling during the vulnerable phase of the cardiac cycle (Q-R' Q-T ratio of 0.6 to 0.85 sec.), but sometimes by VPB's falling outside the vulnerable phase. Other conditions for increased vulnerability are a long ventricular cycle length, Q-T prolongation, and increase in the T-wave amplitude.⁷

The criteria for suppression of VPB's in patients with coronary artery disease or myocardial infarction are: coupling or runs, multifocal origin, 5 or more per minute, and occurrence in the vulnerable phase of the cardiac cycle R T (R on T phenomenon) (Fig. 2).¹ Some clinical studies have been initiated by us^{21, 22} and others in order to define the presence of an abnormal vectorcardiographic pattern of VPB's arising from an ischemic focus, as opposed to that arising from a normal myocardium. This information has particular significance when a patient with myocardial infarction receives an electrical pacemaker.^{23, 24}

Ventricular tachycardia is defined as a succession of 3 or more VPB's at rates greater than 120 beats per min. (150–250 per minute in the original definition of the New York Heart Association). Its identification is made on the basis of bizarre morphology, A-V dissociation, and especially captured and fusion beats. The EKG diagnosis is very difficult.

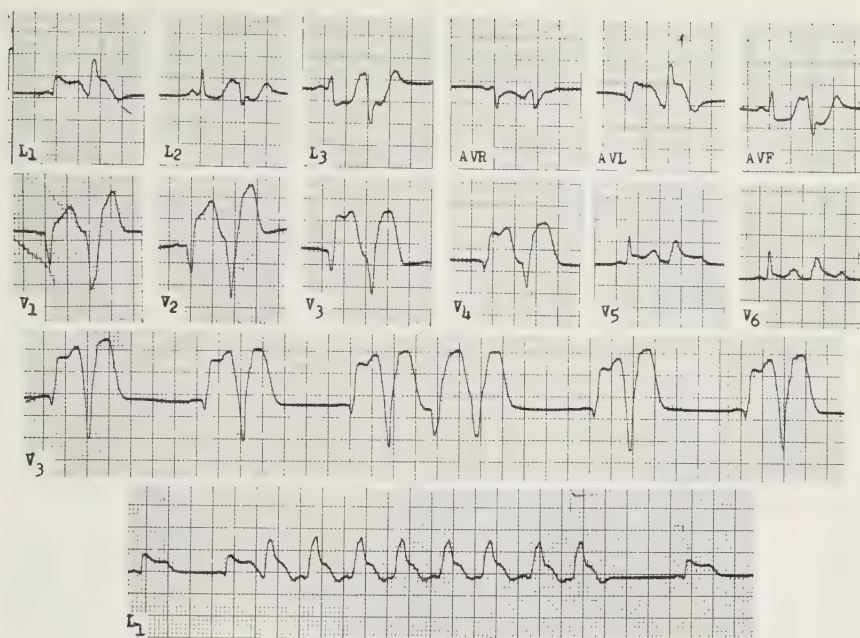


Figure 2. A 46 year old man with acute myocardial infarction first developed bigeminy (R on T phenomenon), then short and long bursts of ventricular tachycardia. He responded to 50 mg. of lidocaine administered intravenously.

Clinical bedside clues are, therefore, of particular value. These include: (1) varying intensity of the first heart sound; (2) wide splitting of both the first and second sounds; (3) atrial, ventricular, and summation gallops; (4) variations in systemic peak blood pressure; and (5) intermittent Cannon waves in the jugular venous pulse. An intra-atrial EKG is helpful in detecting P waves not seen on the surface EKG. The bundle of His recording shows His bundle depolarization to be obscured within each ventricular depolarization and not preceding ventricular activity, in 1:1 ventriculoatrial conduction. The tachyarrhythmia could arise in the His bundle, in the atrium, or in the bundle branches if His bundle depolarization precedes ventricular depolarization.⁶

Ventricular tachycardia of extrasystolic type is initiated by VPB's while the parasystolic type is caused by a "protected" ectopic focus, being rare in coronary artery disease. Accelerated idioventricular rhythm with a rate of 60 to 100 beats per minute is considered a benign arrhythmia that can degenerate into ventricular tachycardia.

Ventricular flutter is differentiated from ventricular tachycardia by some cardiologists by the sine wave appearance, with the QRS and T being symmetric and in mirror-image of each other. The rate is greater than 200 per minute. Ventricular tachycardia reflects a diseased heart, though it has been reported in normal individuals. Brief runs are often seen during cardiac catheterization and angiography, following DC shock, during proper function or malfunction of pacemakers, during

treatment with many drugs (digitalis, sympathetic amines, antiarrhythmic drugs—including quinidine and procainamide—and other drugs), during syncope in patients with Adam-Stokes syndrome, and in myxedema coma.

Ventricular fibrillation occurs in varied situations that overlap frequently with those that cause ventricular standstill (ventricular asystole). It occurs in suffocation, drowning and electrocution, especially when there is an electrical pathway from the external surface of the body to the heart (catheter), with vagal stimulation, Adams-Stokes attacks, and drugs that depress myocardial rhythmicity (quinidine). Ventricular fibrillation can be a terminal event in ventricular tachycardia, especially when depressant drugs are used during anesthesia and surgery. Ventricular fibrillation is commoner than asystole in the cardiac arrest that sometimes follows acute myocardial infarction.¹⁰ Primary ventricular fibrillation occurs unexpectedly in patients with little or no pump failure, while the secondary type occurs as the terminal stage in death from circulatory failure. In one study, primary ventricular fibrillation was detected in 5.5 per cent of patients with myocardial infarction admitted within 4 hours after onset of symptoms, compared with 0.4 per cent when admission was delayed.⁹ Ventricular fibrillation was the invariable cause of abrupt asymptomatic cardiac arrest during EKG monitoring of patients with stable coronary artery disease.¹¹ Since it may well be the cause of most sudden deaths in paced patients,³ a malfunctioning pacemaker should be disconnected by cutting the electrode wires immediately. Prevention of ventricular fibrillation means early and sustained treatment of ventricular irritability, if coronary artery disease is the cause.

Treatment

The treatment of choice in ventricular irritability is *lidocaine*, intravenously, starting with 1 mg. per kg. of body weight or 50 to 100 mg. for the average adult. When necessary, a total dose as high as 5 mg. per kg. can be administered over a 15 to 20 minute period.

For long-term suppression of VPB's, 1 to 4 mg. per min. (1 to 2 gm. in 500 ml. of 5 per cent dextrose in water) or 200 to 300 mg. intramuscularly is recommended. In 88 per cent of the cases, it completely abolishes the ectopic activity. Its onset of action is rapid (15 to 30 seconds) and the duration effect short (20 minutes). Common side-effects are symptoms of central nervous system depression and hypotension. Less frequently it produces sinoatrial arrest, especially in older patients, and (extremely rarely) alarming ventricular acceleration or A-V block. *Procainamide* is started with a loading dose of 750 mg. to 1 gm. followed by 250 to 500 mg. every 3 to 4 hours. Serious adverse reactions may occur, especially after prolonged treatment. These include arthralgia, fever, rash, myasthenia, and lupus-like syndrome.

Quinidine is used in doses of 200 to 300 mg. every 4 to 6 hours. Adverse reactions occur in 30 per cent. *Diphenylhydantoin* is given intravenously, 100 mg. every 5 minutes up to 500 mg.; the oral dose is 100 mg. 3 to 4 times daily. Side effects include lethargy, vertigo, dysarthria, and nystagmus. In a few cases it produced cardiac arrest. *Propranolol* is administered intravenously in doses of 0.5 mg. every 2 minutes up to 3 to

4 mg., with good results appearing in 15 minutes. It is the drug of choice in treating the heritable syndrome of QTc prolongation,¹⁵ with or without deafness and paroxysmal ventricular arrhythmias.

Bretylium tosylate has been used experimentally in tachyarrhythmias. An initial loading dose of 600 mg. with incremental doses of 200 mg. every 1 to 2 hours may be followed, if necessary, by a maintenance dose of 5 mg. per kg. intravenously or intramuscularly. The patient should be kept recumbent because of secondary hypotension.

In many situations a combination of drugs is necessary, taking into account their complementary physiologic properties.

DC shock is frequently used in tachyarrhythmias. One should use the minimum level necessary for conversion of the arrhythmia after administration of diazepam (Valium) or methohexital. Associated administration of lidocaine drip before, during, and after DC shock reduces ventricular irritability (100 mg. of lidocaine in 100 ml. of 5 per cent dextrose in water.) Repeated DC shocks are often necessary (Fig. 3). A thump to the chest may occasionally restore regular sinus rhythm (Fig. 4).

Demand ventricular pacing has been used for several years; atrial pacing has been successfully used⁴ when A-V conduction is intact (reported only recently).

Correction of the metabolic disturbances present in these life-threatening tachyarrhythmias should always be undertaken early.

Cardiac surgery has been successful in correcting a few cases of refractory ventricular irritability due to myocardial aneurysm.

Revascularization of the myocardium, after myocardial infarction, in chronic and several acute situations has opened new avenues to be explored. Once ventricular fibrillation is present, a vigorous blow to the

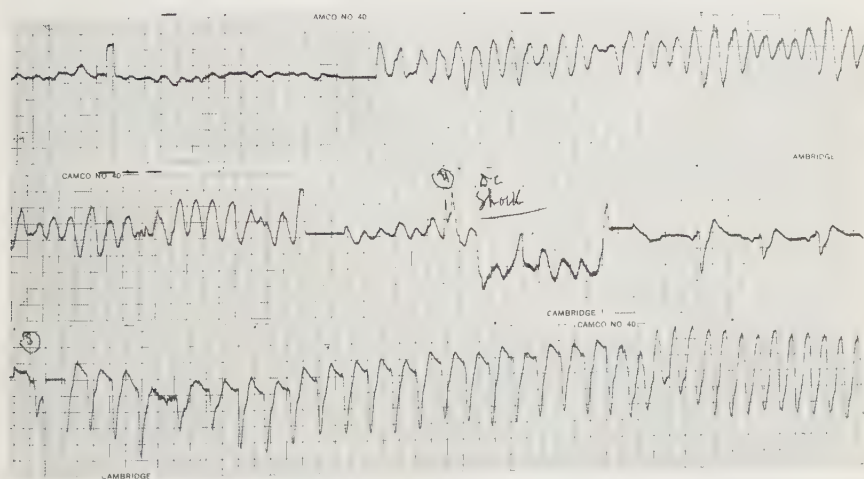


Figure 3. This 54 year old patient with acute anterolateral wall myocardial infarction developed ventricular fibrillation in the emergency room. After DC shock he reverted to regular sinus rhythm and then relapsed in ventricular fibrillation. After intravenous drip with lidocaine and receiving DC shock 6 times he converted to regular sinus rhythm. He left the hospital in good general condition.

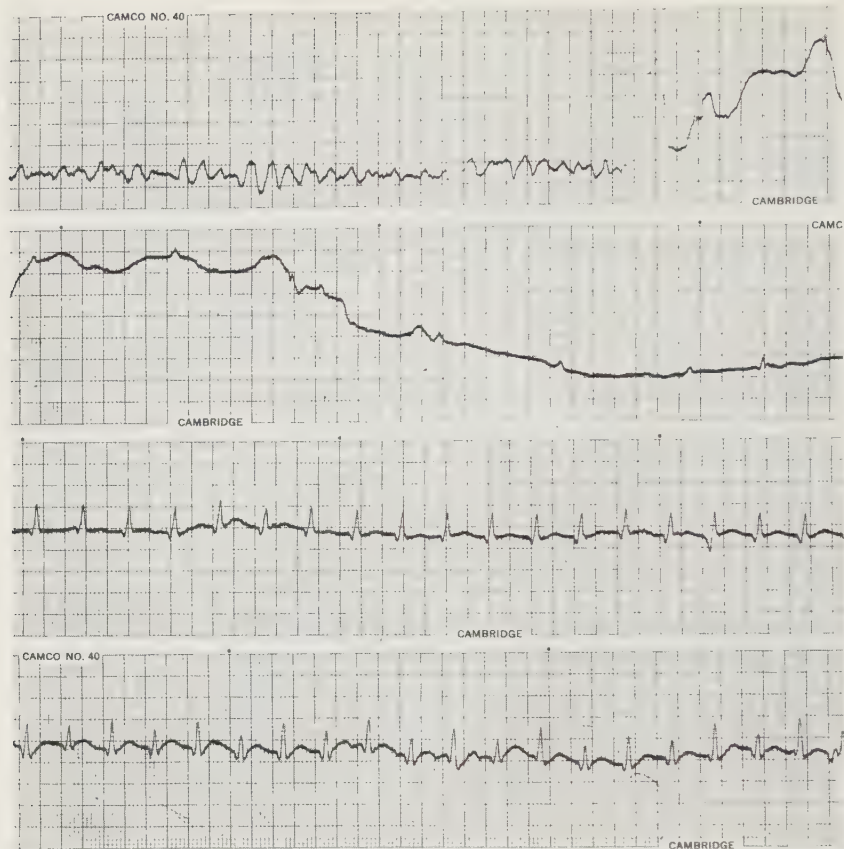


Figure 4. A 44 year old patient had severe chest pain and syncopal attack. The electrocardiogram showed ventricular fibrillation. A thump over the chest induced supraventricular tachycardia with electrical alternance.

chest, electrical defibrillation and the whole classic gamut of means of resuscitation is used wherever it occurs.

BRADYARRHYTHMIAS

A ventricular rate above 50 to 60, in the absence of failure, hypotension, and ventricular irritability, does not require any treatment. Prophylactic treatment may be indicated in postoperative patients with ventricular septal repair, during coronary arteriography and endoscopy² in heart catheterization of patients with fascicular blocks, in drug overdose with digitalis, propranolol, or sedatives, and in hypoxia produced by pulmonary emboli. Severe bradycardia may occur in hyperactive vagotony producing hypoxia, syncope, carotid sinus syncope (spontaneous or after carotid massage), epileptic syndrome, advanced A-V block, and sick sinus syndrome⁵ (Fig. 5).

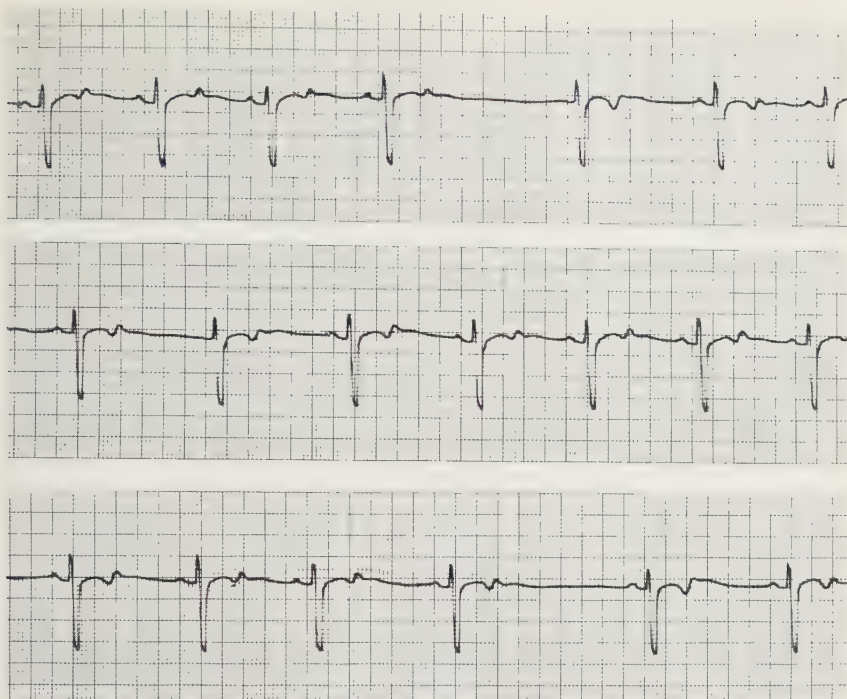


Figure 5. This 72 year old patient was hospitalized because of syncopal episodes. Conventional electrocardiogram was unremarkable. Twenty-four hour Holter monitoring disclosed a sick sinus syndrome with nodal escape beats. After insertion of a demand pacemaker the syncopal attacks disappeared.

The sick sinus syndrome is due either to failure of the sinus node to generate an electrical impulse (marked sinus bradycardia, sinus arrest) or to lack of atrial depolarization—sinoatrial exit block. If a new pacemaker does not take over, periods of cardiac arrest manifested by syncopal episodes may ensue.

Tachycardia may complicate bradycardia—the syndrome of alternating bradycardia and tachycardia.¹⁸ Atropine is tried and, in the absence of evident improvement, a pacemaker is inserted.

In patients with myocardial infarction, sinus or nodal bradycardias are seen in 32 per cent within the first hour of onset, and are more frequent when the inferior wall is involved. Bradycardia and administration of drugs (digitalis, sympathetic drugs, etc.) in the coronary care unit increases ventricular irritability. Cardio-acceleration could be obtained with atropine (1 mg. intravenously) administered with care under continuous monitoring, for serious arrhythmias can follow the use of atropine.¹² Isoproterenol, 0.05 mg. intravenously or 1 mg. per 500 ml. of 5 per cent dextrose in water, and electrical pacing (atrial or ventricular) are currently used for the same purpose.

Failure of the supraventricular impulse to propagate to the ventricle results in A-V block. His bundle EKG determines the anatomic localiza-

tion of the conduction delay at the proximal or distal site of the His bundle; Mobitz type II heart block and third degree A-V block represent life-threatening arrhythmias.

In inferior wall myocardial infarction, a demand pacemaker should be used only when drugs fail to increase the rate to an optimal level, in Mobitz type II and third degree A-V block associated with wide QRS and a ventricular rate below 60 per min, in severe heart failure, or in syncope with A-V block. In anterior wall myocardial infarction, a stand-by pacemaker is indicated in the presence of bundle branch block and shock, left bundle branch block alternating with right bundle branch block, left bundle branch block with first or second degree A-V block, right bundle branch block and first degree A-V block, right bundle branch block and left anterior hemiblock, and right bundle branch block with left posterior hemiblock.

Regardless of the treatment, patients who develop bundle branch block after myocardial infarction have a high mortality inside the hospital and after discharge.¹⁷

ARRHYTHMIAS OCCURRING IN SPECIAL SITUATIONS

Digitalis toxicity presents a special problem since it occurs in as many as 20 per cent of patients receiving the drug. Though digitalis can give any type of arrhythmia, of particular significance are multifocal ectopic beats, ventricular tachycardia appearing as an exit block or bidirectional, atrial tachycardia with block and underlying heart disease²⁵ (Fig. 6), "rapid" atrial fibrillation, or "slow" atrial fibrillation associated with a high degree of A-V block.

If discontinuation of the drug and correction of electrolyte imbalance, hypoxia, and pH (and, when necessary, administration of K^+ , 0.5 to 0.75 mEq. per min. or of 3 doses of 40 mEq. at hourly intervals) is not sufficient, lidocaine, diphenylhydantoin, or propranolol is the drug of choice. Quinidine or procainamide are of lesser use. DC shock, preceded by a small dose of lidocaine, is used in life-threatening situations (Fig. 1). Endocardial pacing is useful in high degree A-V block, ventricular asystole, and complete heart block.

Patients with *cardiomyopathies* may develop life-threatening arrhythmias, often refractory to therapy. At the Queens Hospital Center we have seen severe conduction and rhythm disturbances (ventricular tachycardia, multifocal VPB's, bigeminy, and life-threatening supraventricular arrhythmias) in 42 of 125 patients with advanced primary myocardial disease associated with alcohol intake. In at least 9 patients, sudden death occurred before advanced congestive heart failure developed. A recent report¹⁹ describes ventricular irritability (coupled and runs of VPB's) and syncope after ingestion of alcohol in a patient with a normal heart.

The treatment of life-threatening arrhythmias in these patients should be carried out in the intensive care unit. Antiarrhythmic agents are not always helpful. If necessary, a transvenous pacemaker is inserted. Digitalis should be given with great caution.

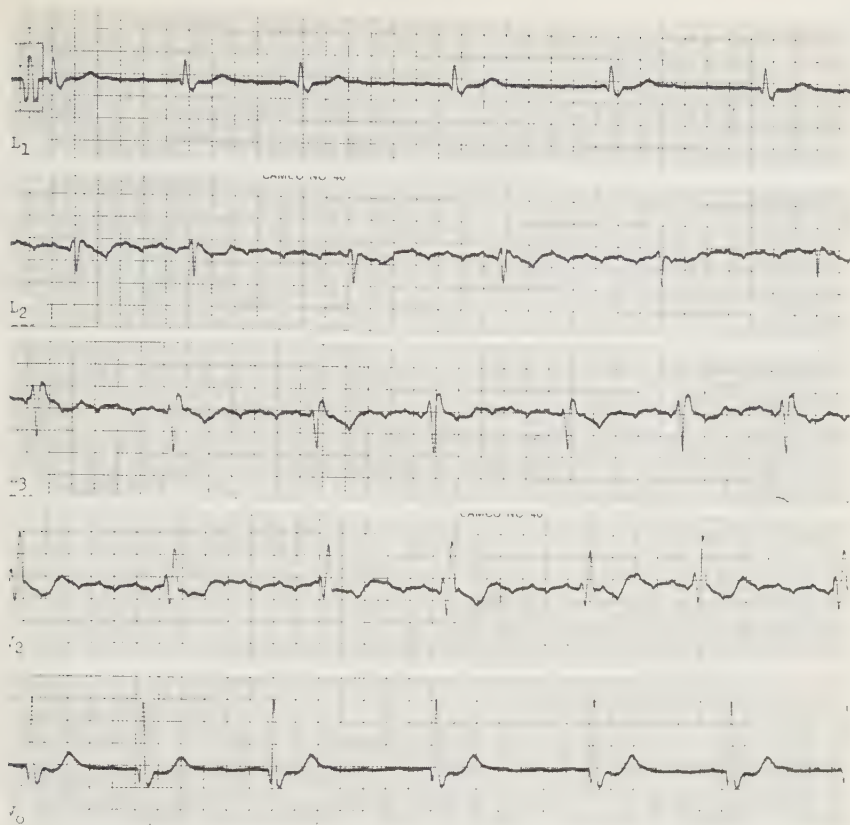


Figure 6. A 93 year old patient with impaired renal function, on digitalis, had atrial tachycardia with high degree of intra-atrial block and varying degree atrioventricular block. (From Zoneraich, S., and Zoneraich, O.: J. Electrocardiol., 4:369, 1971, with permission.)

Sarcoidosis and *neoplastic diseases* may cause life-threatening arrhythmias. Steroids and an electrical pacemaker are the treatment of choice in the former case. Surgical excision of a sarcoidal ventricular aneurysm with good results has been reported by Lull and associates.

Anesthesia and surgery produce a higher incidence of life-threatening arrhythmias during intubation, in the presence of preexisting arrhythmias, during prolonged operations, and in patients who have received digitalis. Patients with mitral stenosis, pheochromocytoma, and cerebrovascular disease present a higher risk than the general surgical population.

Although atropine given during anesthesia can be effective in preventing arrhythmias, when combined with scopolamine, cyclopropane, or halothane it can produce a life-threatening arrhythmia (Fig. 7). As antiarrhythmic agents and cardioversion are being readied, operating room personnel should eliminate excess carbon dioxide, avoid injecting catecholamines, lower the concentration or change the anesthetic agent, and stop surgical manipulations.

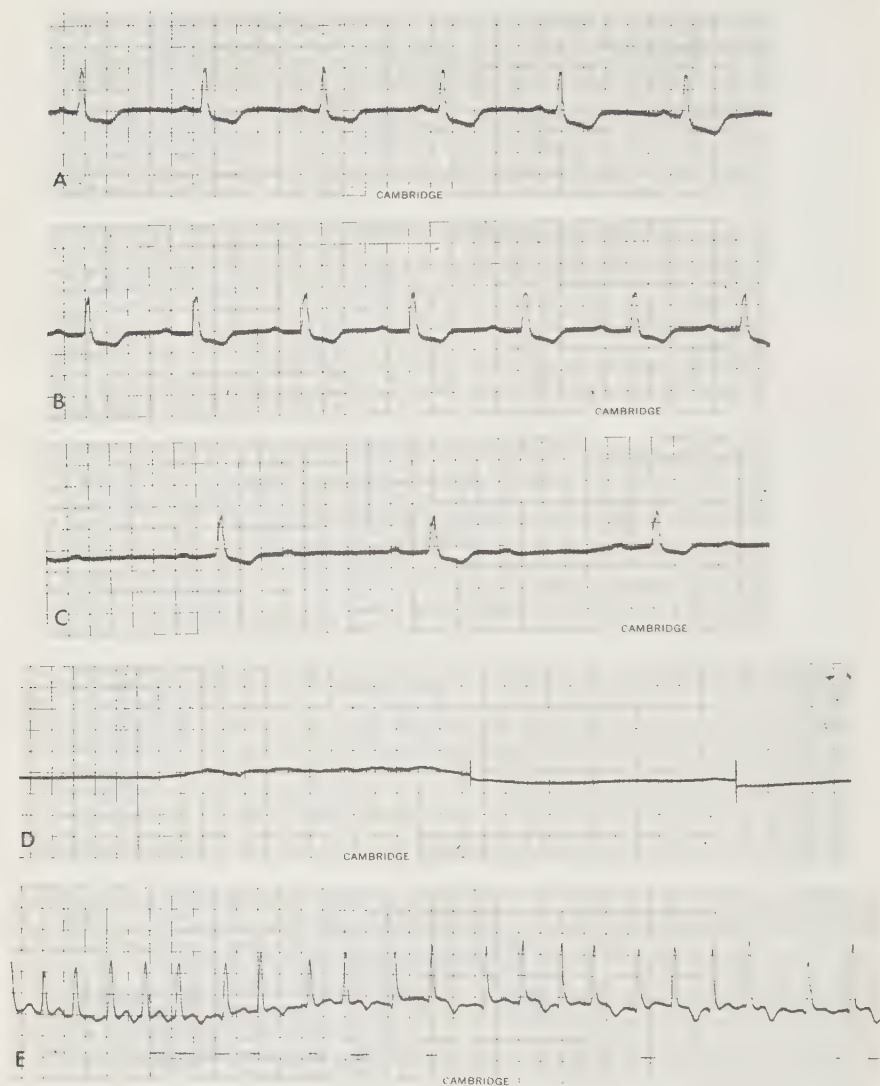


Figure 7. During anesthesia with halothane and nitrous oxide, this 21 year old woman developed first degree (B) and second degree (C) atrioventricular block. Following intravenous injection of 1 mg. of atropine she went into cardiac arrest (D). After resuscitative measures supraventricular tachyarrhythmia developed (E).

Wolf-Parkinson-White syndrome may produce severe paroxysmal arrhythmias that can be life-threatening in middle-aged patients, particularly those with underlying heart disease. In some of the 22 known cases with unexplained sudden death ventricular fibrillation may have been the direct cause. Antiarrhythmic drugs including digitalis (and in some cases atrial pacing) break the arrhythmias. In disabling situations, surgical interruption of the accessory pathway in the *Wolf-Parkinson-White* syndrome, types B and AB, has been performed. In one patient with type A, the accessory pathway could not be sectioned; instead, the patient was left with A-V block, and a pacemaker was implanted.

PREVENTION OF LIFE-THREATENING ARRHYTHMIAS IN CORONARY ARTERY DISEASE

In the hospital setting, mortality from myocardial infarction has been lowered from 30 to 20 per cent, mostly by preventing and treating life-threatening arrhythmias. Taking advantage of the continuous 24 hours EKG tape recording (Holter), and using drug blood levels and double-blind conditions, several studies^{1, 8, 14, 16} have demonstrated that prophylactic administration of procainamide, lidocaine, quinidine, or bretylium tosylate is effective in lowering the frequency of ventricular irritability. The possibility that more than half the patients with extensive coronary atherosclerosis die of life-threatening arrhythmias before reaching the hospital is suggested by the high incidence of ventricular fibrillation at the beginning of the ischemic process, and by its presence in patients with sudden arrest subjected to fortuitous EKG monitoring. Unfortunately, precise evidence is still lacking.

Over the last decade, important steps have been taken to reduce the high mortality in coronary artery disease, consisting of: (1) methods to avoid delay in arrival at the hospital—fixed satellite industrial coronary care units and mobile coronary care units, and (2) methods to shorten the delay in offering medical care. Included in the latter are: Educating the public to pay attention to early warnings; professional education; identification of individuals in the high risk group by ambulatory EKG monitoring; long-term prophylactic therapy; and use of the implantable demand defibrillator.¹³

Lidocaine should be administered (50 mg. bolus intravenously and 200 mg. intramuscularly) whenever a life-threatening arrhythmia occurs outside the hospital, if the ventricular rate is above 50 per minute. Atropine should be used in selected patients under more stringent supervision. Long term prophylactic therapy with procainamide and quinidine is used in survivors of myocardial infarction who have persistent ventricular ectopic activity. Other high risk patients may be added in the future, after proper identification of such groups. Better antiarrhythmic agents, with fewer side effects, will be found long before we learn to prevent atherosclerosis entirely.

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Cardiac Pacemakers

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Cardiac pacing is now the standard therapy for complete heart block and recently has been used in treating other arrhythmias—tachycardias as well as bradycardias. In addition, atrial pacing is used for diagnostic and therapeutic purposes. There now exist many different types of pulse generators of varying degrees of electronic sophistication; with further engineering improvements, and with increasing familiarity with cardiac pacemakers, utilization of these devices will probably continue to proliferate. Because of their widespread use, and because patients with cardiac pacemakers must be followed both for complications associated with their presence and for early detection of pacemaker failure, a brief review of cardiac pacemakers is in order.

TYPES OF CARDIAC PACEMAKERS

All pacemakers consist of a pulse generator, which contains a power source and electronic components, and one or more leads. The leads deliver the pacemaker impulse to the heart, and in some cases conduct electricity from the heart to the pulse generator (Fig. 1). The present approach of choice is the tranvenous positioning of an electrode catheter so that its tip is in contact with the right ventricular wall (Figs. 2 and 3); less often, particularly in the presence of normal A-V conduction, the tip may be placed in the right atrium. The pulse generator is then implanted subcutaneously in the chest wall (Fig. 3). Other approaches to cardiac pacing are also in use.

There are a number of different types of pacemakers (Fig. 1):^{5, 16, 25}

1. The *parasystolic* (competitive, asynchronous, fixed-rate) pacemaker is the oldest type, is generally considered the most reliable, and is the fail-safe mode of operation of the other types. The parasystolic pacemaker stimulates the heart at a fixed rate independent of the heart's own electrical activity. Types of parasystolic pacing include ventricular, atrial, and atrioventricular sequential pacing.

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Figure 1. Implantable pacemakers and an external unit. Catheter electrodes in foreground. (Courtesy Medtronic, Inc.)

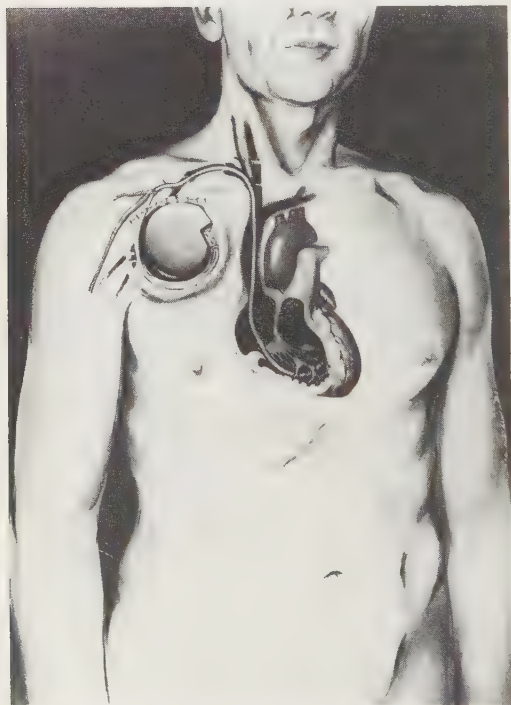


Figure 2. Artist's rendering of implanted pacemaker and catheter electrode in good position. Note that the tip of the catheter is under right ventricular trabeculae. (Courtesy Medtronic, Inc.)

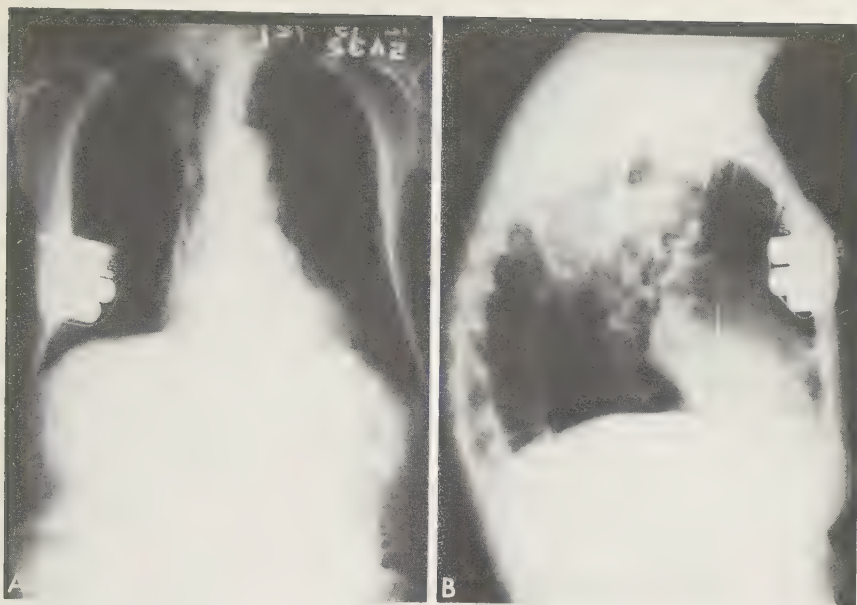


Figure 3. Posteroanterior and lateral chest films. Implanted pacemaker.

2. *Non parasystolic* (non competitive) pacemakers are controlled by the intrinsic electrical activity of the heart. They fall into two groups, demand pacemakers and R-synchronous pacemakers.

The *demand pacemaker* (R-inhibited pacemaker) is constructed so that its pacemaker activity is suppressed by an electrical signal from the heart. In the absence of a QRS complex (or P wave, depending on mode of employ), a stimulus is produced within a preset period. Types of demand pacemakers are: (a) ventricular demand (QRS inhibited, with stimulation of ventricles); (b) atrial demand (P wave inhibited, with stimulation of atria); and (c) bifocal demand (QRS inhibited, atrioventricular sequential pacing). The bifocal demand unit may be thought of as two demand pacemakers in one: a QRS-inhibited ventricular demand unit together with a QRS-inhibited unit that paces the atria.

The *R-synchronous pacemaker* emits an impulse into the absolute refractory period of each QRS complex it senses. In the absence of a signal from the heart, the unit reverts to its own automatic rate and paces. Types of R-synchronous pacemakers are: (a) ventricular synchronous (QRS triggered, with stimulation of ventricles), and (b) atrial synchronous (P wave triggered, with stimulation of ventricles). The atrial synchronous pacemaker may be thought of as an electronic atrioventricular node, complete with normal PR interval and a refractory period to prevent rapid ventricular response to atrial tachyarrhythmias.

There is no general agreement about which type of pacemaker is ideal. However, the nonparasystolic (noncompetitive) pacemakers have become the most generally used. Of patients with complete heart block who are paced, 25 per cent develop normal conduction,¹¹ and competition

occurs with a fixed-rate pacemaker. By avoiding this competition, the nonparasystolic units prevent the pacemaker spike from falling into the vulnerable phase of cardiac cycle and thus setting off fatal ventricular arrhythmias (either observed or inferred from sudden unexplained death in paced patients³¹). However, ventricular arrhythmias have occurred in patients with noncompetitive pacemakers, and no differences in the frequency of sudden unexplained death have been noted in some series.^{17, 37} Certain patients must be paced in a noncompetitive mode. These include individuals whose threshold for ventricular fibrillation has been lowered by myocardial infarction or ischemia, by medications such as digitalis or sympathomimetic amines, or by electrolyte disturbances. Patients with intermittent conduction should also be paced only in the noncompetitive mode.

Although most pacemakers used have been ventricular units, there has been a recent increase in interest in atrial pacing for therapeutic and diagnostic purposes.^{7, 9, 35} These units may be used to treat, in the presence of normal atrioventricular conduction, symptomatic bradyarrhythmias of sinus or atrial origin, and refractory supraventricular or ventricular tachycardias. Diagnostic uses of atrial pacing include study of patients with angina, study of atrioventricular conduction (often in conjunction with His bundle electrocardiography), and study of patients with mitral stenosis to assess the degree of myocardial contribution to disability. The use of a J-shaped catheter or fixation of the atrial electrode in the coronary sinus has provided fairly stable lead positioning, but there is a 20 per cent failure rate in long term atrial pacing, because of either catheter displacement or exit block.²⁴

Where temporary pacing is planned, the pulse generator is an external battery-powered unit. Where permanent pacing is desired, the pulse generator is a subcutaneously implanted battery-powered unit. (Both types are shown in Fig. 1.) Radiofrequency units and induction-coupled units have been developed for permanent pacing with externally worn pulse generators, but are not in common use in this country.³⁴

With some exceptions most leads are inserted transvenously. The leads may be bipolar, with cathode and anode in the heart; or unipolar, with the cathode placed in the heart and the anode generally located on the pulse generator. Each type of lead system has pros and cons, but in the clinical setting either is acceptable.³⁴

INDICATIONS FOR USE OF A PERMANENT PACEMAKER^{5, 8, 13}

Complete Heart Block

Symptomatic complete heart block is the most generally accepted indication for permanent pacing. The symptoms commonly observed are Stokes-Adams attacks and symptoms caused by decreased cardiac output with subsequent poor organ perfusion. The Stokes-Adams attack is the most dramatic symptom of heart block, is usually due to asystole, and is abolished when proper pacing is achieved. One may also observe in pa-

tients with complete heart block symptoms of congestive heart failure and prerenal azotemia, as well as lethargy, forgetfulness or light-headedness. To the degree that these symptoms, attributable to decreased cardiac output and poor organ perfusion, are caused by the slow heart rate, they will be corrected by correction of the bradycardia. For example, it has been shown that in patients with complete heart block and congestive heart failure, use of a pacemaker will increase the resting cardiac output 50 to 80 per cent; moreover, 50 to 85 per cent of these patients will become compensated with no other treatment.^{3, 13}

Asymptomatic complete heart block. There is no universal agreement about the use of a pacemaker in the asymptomatic patient with complete heart block, but such therapy is probably indicated. These patients do not actually remain asymptomatic for long: two-thirds of all new cases of complete heart block will develop Stokes-Adams attacks.³⁰ *Mortality in the first year after diagnosis of complete heart block is 50 per cent*, with most deaths occurring early and with prognosis not strikingly related to the presence or absence of Stokes-Adams episodes.^{12, 21} With use of pacemakers, *survival* for the first year after diagnosis is 80 to 89 per cent.^{6, 21, 37}

Symptomatic Atrioventricular Block Other than Complete Heart Block³⁰

Second degree heart block with syncopal episodes or congestive heart failure. It should be noted that patients with second degree heart block of the Wenckebach type generally do not require pacemakers, while those with Mobitz type II may.¹²

Symptomatic bifascicular blocks: (1) right bundle branch block with left axis deviation; (2) bundle branch block with first degree heart block; and (3) alternating left and right bundle branch block.

Symptomatic Bradycardias of Other Etiologies^{7, 8, 9, 36}

These include sinus bradycardia, nodal bradycardia, sinus arrest or sino-atrial block, and "sick sinus syndrome." In this syndrome, with its alternations between bradycardia and tachycardia, the pacemaker will maintain heart rate during the bradycardia but will not prevent tachycardias. However, the pacemaker allows treatment of the tachycardias with appropriate medications without the danger of asystole.

It should be noted that the key word is *symptomatic*, and that the decision to pace is based on clinical findings.

Other indications for use of a permanent pacemaker include supraventricular and ventricular tachycardias refractory to drug therapy,^{20, 23, 21, 28} arrhythmias complicating the Wolff-Parkinson-White syndrome, arrhythmias following cardiac surgery, and arrhythmias resulting from digitalis toxicity that cannot be otherwise treated. In treating many of these, the pacemaker may be used alone or in combination with medication. Pacing may be especially helpful in preventing bradycardia or asystole resulting from concomitant use of cardiosuppressive drugs. The pacemaker used may be atrial or ventricular. A trial on a temporary pacemaker should precede implantation of a permanent unit.

THE PACEMAKER IN ACUTE MYOCARDIAL INFARCTION

The overall hospital mortality in acute myocardial infarction, which is 25 per cent, rises in the presence of any degree of atrioventricular conduction disturbance. With complete heart block the mortality rises to 45 per cent, and to 100 per cent when this conduction disturbance complicates a second infarction.⁴ Of all patients with complete heart block and myocardial infarction (representing 4 to 7 per cent of myocardial infarctions), 55 per cent have inferior wall infarction and 17 per cent have anterior wall infarction.⁴ In patients with myocardial infarction who manifest first degree A-V block, 45 per cent have no further progression of the conduction defect, 22 per cent progress to second degree block only, and 22 per cent progress to complete heart block. Of patients who manifest second degree A-V block, 32 per cent progress to complete heart block.

Because of differences in pathophysiology and prognosis, the atrioventricular blocks complicating anterior wall and inferior wall myocardial infarction should be considered as two different entities.

Heart Block Complicating Inferior Wall Myocardial Infarction^{22, 27, 30, 33}

In inferior wall myocardial infarction the atrioventricular node is involved by edema or ischemia, but is rarely necrosed. If complete heart block occurs, onset is usually during the first day of infarction (rarely after the fourth day), and is often preceded by conduction disturbances of lesser degree—especially second degree A-V block of the Mobitz I variety. The subsidiary pacemaker is usually “high up;” accordingly, the QRS complexes tend to be narrow and the heart rate relatively rapid. Normal conduction usually recurs within 1 week. Isoproterenol and atropine are often effective in treatment. In the absence of shock or of wide QRS complexes mortality is similar with or without heart block (about 25 per cent); death as a result of bradycardia or asystole is rare, even if the patient is not paced. However, in the presence of shock, or if the QRS complexes are wide, prognosis is poor even with pacing.

Heart Block Complicating Anterior Wall Myocardial Infarction^{22, 27, 30, 33}

In anterior wall myocardial infarction there is extensive and irregular necrosis that involves both bundle branches, usually resulting in complete destruction of the right bundle and partial destruction of the left. The resulting heart block, therefore, is caused by necrosis of both bundle branches. The subsidiary pacemaker is low in the ventricle, the QRS complexes are wide, and the heart rate is slow. The onset of complete heart block is sudden and unpredictable, but may be preceded by evidence of bifascicular block or by second degree heart block, usually Mobitz II. The mortality in anterior wall myocardial infarction complicated by complete heart block is 80 per cent, with death usually occurring early—29 per cent within 2 hours of onset, 83 per cent within 72 hours. Death, however, is usually due not to arrhythmia but to shock because of pump failure; generally, pacing makes little difference in survival.

From all this it may be surmised that pacing has little effect on the prognosis of a patient with myocardial infarction complicated by complete heart block. However, a 10 per cent overall salvage has been estimated;¹⁰ moreover, statistics cannot be applied to an individual patient. Accordingly, pacemaker therapy is indicated under the following conditions:

1. Complete heart block with deterioration of the patient's condition because of bradycardia.

2. Complete heart block with life-threatening arrhythmia, either ventricular asystole or ventricular tachyarrhythmia.

3. Potential heart block – bundle branch block or second degree atrio-ventricular block.

4. Bradycardias other than those due to A-V block.

5. Tachyarrhythmias, supraventricular or ventricular, refractory to other forms of therapy.

In approximately 5 per cent of those who survive complete heart block with myocardial infarction, the block persists.²⁹ These individuals should be considered for a permanent pacemaker.

COMPLICATIONS ASSOCIATED WITH PACEMAKER THERAPY^{14, 19, 26, 38}

The patient with a cardiac pacemaker must be followed at routine intervals. He should be seen 1 month after implantation, at which time the operative site and functioning of the pacemaker should both be checked. Thereafter, the patient may be seen every 6 months for 18 months, and then at 3 month intervals.

The standard office EKG machine may be used to assess pacemaker function and the need to replace the pulse generator or the electrode. Total failure to pace, or intermittent pacing, or loss of synchrony in a synchronous unit is easily recognized. More subtle changes should be sought, however, as these indicate impending battery failure. These changes include a change in pacemaker rate of 10 per cent or more, or a change in the pacemaker spike amplitude or direction. However, because the EKG machines in common use are often not sufficiently precise to show small but important changes in the pacemaker spike, it may be elected to have the patient followed at a pacemaker clinic or by a trans-telephone clinic to detect impending battery failure.

Malfunction of the pulse generator may be due to battery failure (which is the most common cause of malfunction, especially late malfunction, and is the complication which most follow-up efforts are directed to detect); component defects, usually involving transistors; or internal short-circuiting.

Malfunction of leads and electrodes may be due to improper connection of leads to the pulse generator, lead fractures, or displacement of the transvenous endocardial electrode. This last complication is not uncommon. After the leads have been in position for a period of time, intracardiac fibrous adhesions will maintain them in position. Complications of

lead or electrode malfunction include perforation of the heart by an endocardial lead and tachyarrhythmia caused by mechanical pressure of the endocardial electrode.

Myocardial factors contributing to pacemaker complications include increased threshold to local stimulation (exit block), and increased electrical resistance.

Other factors contributing to pacemaker complications are local infections, competition between the pacemaker and the heart, and malfunction resulting from external electrical stimuli.¹ The fixed-rate pacemaker is little affected by external stimuli except for electrocautery used within inches of the unit, and diathermy applied to the pacemaker site. Noncompetitive pacemakers, however, are susceptible to external signals that may be confused with QRS complexes by the sensing circuits. The heart rate may slow if the pacemaker is a demand unit, or become more rapid if the pacemaker is of the R-synchronous type. These electrical hazards are uncommon causes of malfunction and are amenable to advances in engineering.

As has been noted, battery depletion is the commonest cause of pacemaker malfunction. Different pacemaker models have different projected battery life-spans, which may be obtained from the manufacturer. Most units are replaced routinely after 30 months of use, or at such time that study indicates early battery depletion (but before the pacemaker becomes inoperative). Impending failure may be inferred from a standard EKG tracing if there is a change in magnitude or direction of the pacemaker spike, if synchronization is lost, or if there is a change in rate of the pacemaker. The intrinsic rate of noncompetitive pacemaker may be assessed by converting it temporarily to a fixed-rate mode by means of a magnet held close to the pulse generator. Most EKG machines, however, are not reliable indicators of the small rate changes to be studied.

Recently, pacemaker clinics^{18, 32} have been established for very careful follow-up of patients with permanent pacemakers. At such a clinic a modified lead I is recorded from the patient, with the right arm electrode over the site of the pulse generator. The pacemaker impulse is studied by being fed into an electronic counter that measures pacemaker rate in milliseconds, and the amplified impulse fed into an oscilloscope and photographed. From the photograph, amplitude and duration of the pacemaker spike are measured. When battery depletion occurs, pacemaker rate, pulse duration, and amplitude usually become altered simultaneously—indicating the need for replacement of the generator. If two of the three are altered, the generator is still replaced. Loss of synchronization is similarly regarded as evidence of battery failure. Lead failure, or failure of an electronic component in the generator, cannot be predicted. However, should these be causes of pacing failure, characteristic alterations in the pacemaker artifact will be observed.

A less elaborate method of follow-up is the transtelephone clinic,¹³ a central location to which the pulse artifact is transmitted and pacemaker rate assessed by means of an electronic counter. Rate change alone is then used as the criterion for replacement. When a rate change is observed, the rate and output of the pulse generator are characteristically unstable, and the time of total failure becomes unpredictable.

NEW PATHWAYS

At this time, promising areas of research for improvement of pace-makers including operative approaches other than thoracotomy to achieve more stable electrode positioning; improved electrodes; better power sources, including nuclear powered units, biogalvanic cells, and other types of cells; microminiaturization; and better understanding of the physiology of the electrode-heart interface.

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The Diagnosis and Management of Arterial Aneurysms

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A true aneurysm is a localized arterial dilatation resulting from weakening and stretching of the vessel's walls. In most cases, aneurysm formation is a local exaggeration of the normal aging process (arteriosclerosis), in which atrophy of smooth muscle and degeneration of elastic tissue occur in the media of the vessel. The presence of a stenosis or sharp bend in the arterial tree abets this process by decreasing laminar flow and increasing lateral pressure.

The frequency of this lesion is illustrated by a review of 7642 autopsy records in which Fomon et al.⁹ found evidence of 249 aneurysms of the aorta or its major branches (3.3 per cent). In subjects over 25 the incidence was 4.5 per cent, exclusive of peripheral aneurysms. The abdominal aorta was most often involved (77 cases), followed by the ascending aorta (55 cases).

Once established, an aneurysm is subject to a vicious cycle of increased turbulence and further pressure on its weakened walls. The likelihood of aneurysmal rupture depends on location, supporting structures, systemic blood pressure, and longevity of the patient. This report will review the clinical presentation, complications, and indications for surgical repair of the more common aneurysms.

ANEURYSMS OF THE THORACIC AORTA

Arteriosclerosis is now the major cause of aneurysms throughout the thoracic aorta. In a review of the Mayo Clinic's experience with thoracic aneurysms, Joyce et al.¹³ in 1964 listed arteriosclerosis as the cause in 78 of 107 lesions (73 per cent), and lues in 19 per cent. Syphilis involves only the ascending aorta. Other causes include blunt trauma to the chest (5 per cent), post-stenotic dilatation distal to aortic valvular stenosis, and Marfan's syndrome. Congenital aneurysms, which are rare, are usually located near the ligamentum arteriosum.

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Few patients with thoracic aneurysms have pain (17 per cent in the Mayo Clinic Series), and most often the diagnosis is made accidentally by routine chest x-ray. However, there are helpful signs and symptoms in some cases (Table 1). A relatively early clue to the presence of an aneurysm in the *ascending aorta* may be an early decrescendo diastolic murmur of aortic insufficiency associated with a loud and often drum-like aortic closure sound, in contrast to the diminished or absent sound of valvular aortic incompetence. The murmur, secondary to aortic ring dilatation, is often heard best at the aortic area and to the right of the sternum rather than at Erb's point. Some patients may have only a loud aortic sound and a nonspecific ejection murmur. The aortic insufficiency becomes clinically significant in only a minority of patients.

Large aneurysms of the *transverse aorta* are more likely to cause signs and symptoms because of their location in the superior mediastinum. In addition to pain, they may cause dyspnea, cough, and stridor because of tracheal compression; hoarseness by involving the recurrent laryngeal nerve; dysphagia, weight loss, and anemia through esophageal obstruction; and superior vena cava syndrome. With these symptoms and appearance of a mediastinal mass on chest x-ray, it is not uncommon for a transverse aortic aneurysm to be mistaken for neoplastic disease (Fig. 1). In asthenic individuals, it may be possible to palpate the increased pulsation of asymptomatic large transverse and ascending aneurysms along the upper sternal border or inferior to the left clavicle. Palpation is best accomplished with the patient leaning forward. Aneurysms of the *descending aorta* are most treacherous because of complete silence until rupture. Even when they occasionally erode into thoracic vertebrae, they may be painless.

Not surprisingly, arteriosclerotic thoracic aneurysms tend to be associated with diffuse arterial disease. In the Mayo Clinic Series,¹³ 11 patients had abdominal aneurysms, and the incidences of coronary, cerebrovascular, and peripheral arterial diseases were also high. Of great etiologic importance is the presence of long-standing hypertension in the majority of these patients.

The most important laboratory test is the chest roentgenogram, taken in several views. With lateral and oblique views one can often distinguish between a true aneurysm, generalized aortic ectasia, and a mediastinal tumor (Fig. 2). However, serious mistakes are possible, so that further confirmation of the diagnosis is mandatory. Fluoroscopy may demonstrate the expansile nature of the mediastinal shadow, but one must be wary of a transmitted aortic pulse through a nonvascular tumor. Therefore, unless the fluoroscopic findings are classical, it is advisable to confirm the presence of an aneurysm with an angiographic procedure. If surgical repair is contemplated, aortic catheterization is required in order to delineate clearly the size and extent of the aneurysm and to visualize properly the brachiocephalic arteries.

If surgery is not under consideration, aortography after the intravenous injection of radiopaque material or a radionuclide such as technetium-99 will usually suffice. Whenever there is uncertainty in distinguishing between neoplasm and aneurysm, the angiogram should be

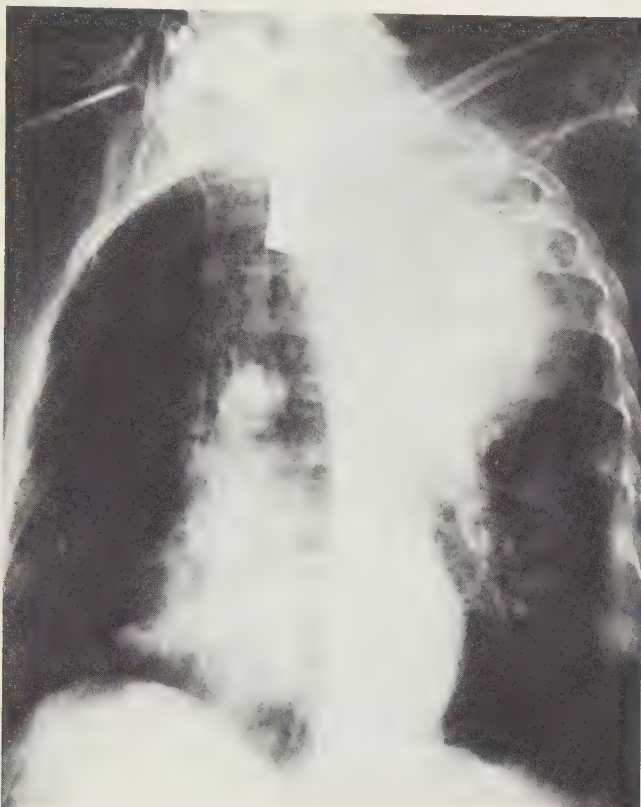


Figure 1. A large aneurysm of the transverse and descending thoracic aorta simulates a neoplastic lesion. Patient presented with respiratory distress.

done first, rather than procedures such as bronchoscopy and esophagoscopy, which might injure a dilated contiguous aorta.

Decisions concerning therapy are difficult, as medical treatment is limited. Lues can be treated with penicillin, and hypertension can be controlled, but the vicious cycle of aneurysmal expansion continues. A decision for or against surgical repair depends on adequate knowledge of surgical risks, natural history of the lesion, and likely longevity of the patient. The only modern prospective data on conservatively treated patients come from the Mayo Clinic Series.¹³ Of 98 patients traced, 49 (50 per cent) were still alive 5 years after initial diagnosis as compared to an expected rate of 90 per cent for the normal population of the same age; 30 per cent survived 10 years. Where the cause of death could be ascertained, 32 per cent died of ruptured aneurysm, and the remainder succumbed to other arteriosclerotic disease. Shape and location of the aneurysm had no effect on the outcome, but mortality was approximately twice as high for symptomatic lesions and those over 6 cm. in diameter as for the smaller lesions. In the retrospective autopsy studies of Fomon and associates,⁹ only one of 84 aneurysms under 5 cm. in diameter was rup-



Figure 2. Lateral roentgenogram of the chest demonstrates an aneurysm of the ascending aorta.

tured, whereas the rupture rate was 15 per cent for those between 5 and 10 cm. and rose to 43 per cent for those over 10 cm.

Surgical techniques for handling the thoracic aorta and providing extracorporeal perfusion have improved, but replacement of the thoracic aorta with a prosthetic graft still carries a high mortality rate even for experienced cardiovascular surgeons in specialized centers. In resection of the ascending or transverse aorta, adequate circulation must be maintained through both carotid arteries, at least one vertebral artery, and arteries supplying the lower portion of the body (especially the kidneys and spinal cord). Total cardiopulmonary bypass is employed. In the case of ascending aortic aneurysms, the aortic valve may also have to be replaced. In the transverse aorta, surgery is particularly hazardous because the origins of the brachiocephalic vessels must be inserted into the prosthesis. Recent published mortality rates for elective resection vary from 17 per cent for the ascending aorta¹⁴ to 20 to 40 per cent for the transverse aorta.⁵ Surgery in the descending aorta is less hazardous, but partial bypass (left atrium to femoral artery or femoral vein to femoral artery with a pump oxygenator) is still required. A surgical mortality rate of 11 per cent has been reported for this location.⁷

It seems prudent to treat patients with small aneurysms conservatively, following them with serial chest x-rays at 3 to 6 month intervals. On the other hand, patients with large, symptomatic lesions, especially expanding ones and those in the descending aorta, should be considered for surgery if their general medical condition allows. One must remember, however, that patients with coronary artery and cerebrovascular disease poorly tolerate major vascular surgery with its attendant blood loss, hypotension, and manipulation of the extracranial cerebral arteries. In short, the decision on surgical repair must be made on an individual basis.

DISSECTING ANEURYSM

Dissecting aneurysm of the thoracic aorta is really a hemorrhage into the media of a previously normal-sized vessel rather than a true aneurysm. The pathology consists of cystic medial necrosis followed by an intimal tear and the formation of a false channel. The lesion is often associated with connective tissue diseases such as Marfan's syndrome in the early decades, and long-standing hypertension is present in two-thirds of the cases in the later decades. Dissection can produce a variety of syndromes, depending on the course and extent of the medial column of blood. The column may re-enter the lumen through a second intimal tear; it may move antegrade or retrograde through the aorta; it may dissect into and compress primary branches of the aorta; and it may rupture through the adventitia at any time or into the pericardial cavity.

About half the patients present with severe chest and back pain, often in association with aortic insufficiency.¹² In some cases, the presenting complaints are related to severe congestive heart failure secondary to aortic incompetence and myocardial ischemia. Regional ischemia of major aortic branches may predominate in the clinical picture. Thus, this lesion must be considered in the differential diagnosis of carotid artery occlusions, renal and mesenteric infarction, myocardial infarction, and acute aorto-iliac obstruction. The appearance of aortic insufficiency in association with chest pain or loss of a major pulse should be considered evidence of dissection until proven otherwise. A myocardial infarction or stroke in association with a wide aortic shadow is also suspect. Occasionally dissection with re-entry is an asymptomatic process, discovered later because of an aortic diastolic murmur or on a routine chest x-ray film. Even the latter may not be striking (Fig. 3).

Prognosis of acute dissection is poor, about 50 per cent of patients dying within 1 week, 75 per cent within a month, and 85 per cent within a year. Emergency aortography is mandatory when this diagnosis is suspected in order to confirm it and to endeavor to locate the primary intimal tear. Medical therapy consists of rapidly lowering the blood pressure to normal levels (120 mm. Hg systolic, 80 diastolic) with a ganglionic blocking agent administered intravenously, and then maintaining it at this level with agents such as guanethidine, reserpine, and α -methyldopa, which diminish the force of ventricular contraction. Although long-term data on the efficacy of this therapy are not yet conclu-

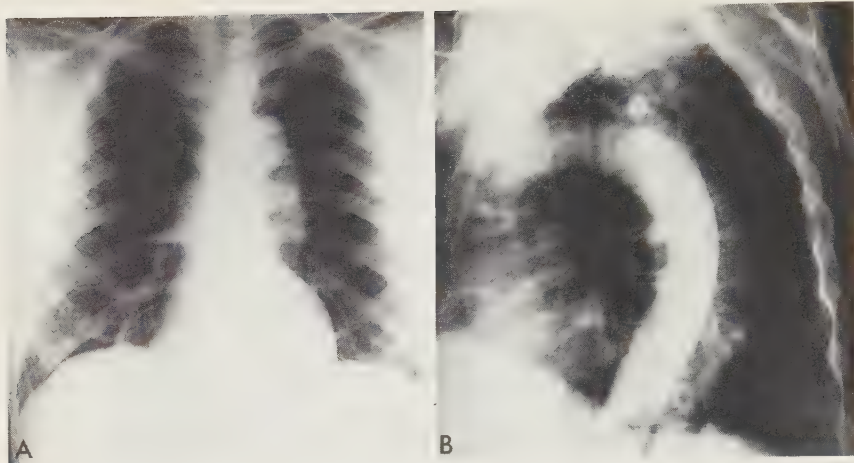


Figure 3. A, Posteroanterior roentgenogram of the chest reveals only mild prominence of the aortic shadow along the left border of the mediastinum. B, An aortogram in the same patient reveals extensive dissection distal to the left subclavian artery (opacified false channel).

sive, several groups have reported striking increases in long-term survival rates with strict control of blood pressure.^{15, 17} In the latest report, 52 per cent were alive after a mean follow-up of 43 months.¹⁵ These patients must be followed at close intervals with electrocardiograms, chest x-rays, and blood urea nitrogen or serum creatinine levels. Acute tubular necrosis, myocardial infarction, cerebrovascular accidents, postural hypotension, and congestive heart failure may result from this therapy.

The development of a saccular aneurysm, severe regional ischemia, and wide-open aortic insufficiency with congestive heart failure are ominous signs and demand rapid surgical intervention (Table 1).

ANEURYSMS OF THE ABDOMINAL AORTA

The abdominal aorta is the most frequent site of aneurysm formation. More than 98 per cent are located distal to the renal arteries, and the majority involve the terminal portion of the aorta and often the origin of the common iliac arteries. Since arteriosclerosis is the cause of almost all abdominal aortic aneurysms, they tend to develop predominantly in the later decades, rarely before the sixth decade and usually in the seventh and eighth decades. The reported male:female ratio varies from 5:1 to 9:1.

The abdominal aneurysms tend to be silent lesions until rupture occurs. Most are discovered accidentally, either on routine physical examination or during a radiologic procedure performed for an entirely different reason. Retrospectively, one may extract some mild symptoms from about one third of these patients on close questioning.¹⁰ They may recall nonspecific, mild abdominal or back discomfort or perhaps a sense of pulsation in the abdomen. If a patient complains of significant back or abdominal pain, aneurysmal rupture is usually imminent.

Table 1. Thoracic Aortic Aneurysms

	LOCATION	USUAL ETIOLOGY	USUAL MODE OF PRESENTATION	POSSIBLE SEQUELAE BEFORE RUPTURE	INDICATIONS FOR SURGERY	MEDICAL THERAPY
True aneurysms	Ascending	1. Arteriosclerosis 2. Lues	Chest x-ray abnormality	Aortic insufficiency	1. Large expanding lesion 2. Severe aortic insufficiency	1. Control hypertension 2. Treat lues
	Transverse	Arteriosclerosis	Chest x-ray abnormality	Compression of mediastinal structures	Large lesion, especially if symptomatic	Control hypertension
	Descending	Arteriosclerosis	Chest x-ray abnormality	Vertebral erosion	Large lesion	Control hypertension
Dissecting aneurysm	Throughout thoracic aorta	Cystic medial necrosis followed by formation of false channel	1. Chest and back pain in 40-50% 2. Neurologic symptoms 3. Congestive heart failure 4. Shock and cardiac tamponade 5. Occasionally as chest x-ray abnormality	1. Aortic insufficiency 2. Regional ischemia 3. Shock 4. Saccular aneurysm	1. Pericardial tamponade 2. Severe aortic insufficiency 3. Significant regional ischemia 4. Saccular aneurysm formation	1. Hypotensive therapy 2. Decrease myocardial contractility

With careful palpation in the epigastrium, the aortic pulse can be detected in most nonobese individuals. When this pulsation becomes prominent and is associated with an expansile mass, the diagnosis of aneurysm is generally obvious. Although an occasional retroperitoneal tumor can simulate an aneurysm by transmitting the aortic pulse forcefully, this is uncommon and has probably been overemphasized. In some patients only a strong pulsation, without a mass, is palpable, and it may be difficult to distinguish between generalized ectasia and tortuosity of the abdominal aorta and a true aneurysm. If the aorta deviates rather sharply to the right or left upper quadrant or if the aortic pulse is well appreciated below the umbilicus, the presence of an aneurysm is likely. Approximately 50 per cent of the aneurysms are associated with a short systolic bruit, but this can also occur with a tortuous aorta. When one considers that rupture of abdominal aortic aneurysms may be responsible for death in one in 250 people over the age of 50,¹⁶ it becomes apparent that palpation of the abdominal aorta is one of the key maneuvers in examination of the middle-aged and elderly population.

The most helpful laboratory test for confirming the diagnosis is a trans-table lateral roentgenogram of the abdomen taken with bone technique. Because of heavy calcification in the aortic wall, two thirds to three fourths of abdominal aneurysms can be visualized in this way. By locating the posterior border along the lumbosacral spine and the anterior wall, one can usually judge the size, location, and extent of the aneurysm quite accurately (Fig. 4). Aortography is usually unnecessary for diagnosis. In fact, the plain film frequently affords a better estimate of the extent of the aneurysm than an aortogram because mural thrombi tend to decrease significantly the size of the opacified lumen. Aortography is occasionally necessary for determining whether the aneurysm extends above the renal arteries.

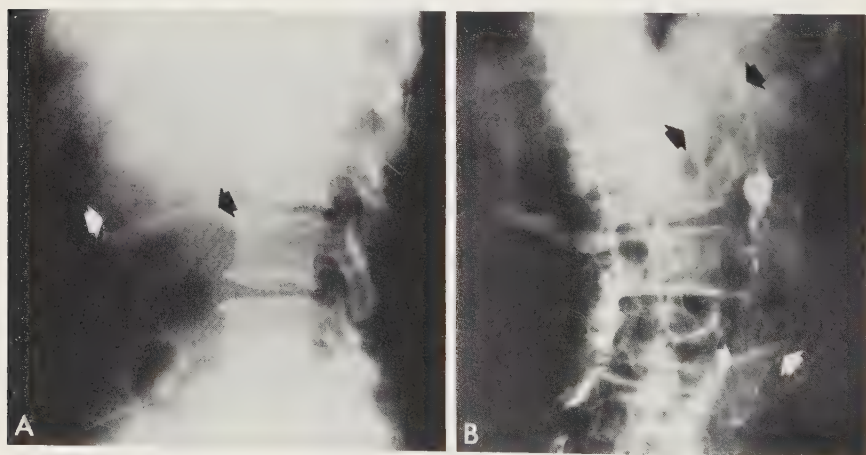


Figure 4. A, A large abdominal aortic aneurysm in the lower abdomen is outlined by its calcified walls. B, Lateral roentgenogram obtained during intravenous pyelography demonstrates multiple areas of aortic dilatation. The major aneurysm is superior to the kidneys.

Patients with abdominal aneurysms tend to have generalized cardiovascular disease. In one series, 47 per cent had definite coronary artery disease; 43 per cent, peripheral arterial obstruction; 8 per cent, cerebrovascular disease; and 34 per cent, hypertension.¹⁰ Nevertheless the findings in longitudinal studies of patients with this lesion argue strongly for an aggressive approach. The 5 year survival rate from the time of initial diagnosis for untreated patients has varied from 17.2 to 36.4 per cent.² Approximately half the deaths are caused by aneurysmal rupture. Several groups have shown that aneurysmectomy prolongs life. DeBakey et al.⁶ reported that 72 per cent of patients who had undergone resection were alive 3 years after surgery, and 58 per cent after 5 years. Szilagy and co-workers² compared untreated and treated patients after excluding those with advanced age, hypertension, and heart disease, and found a doubling of life expectancy in the operated group. Mortality rate for elective aneurysmectomy has fallen. DeBakey and co-workers⁶ had a 9 per cent operative mortality rate in 1964; in 1966 a 4 per cent rate was reported in a group of patients of whom 88 per cent had other cardiovascular disease.¹⁰

Close attention should be paid to the blood pressure, central venous pressure, and urine output during and after surgery. Continuous electrocardiographic monitoring is advisable because arrhythmias and silent myocardial infarcts are not uncommon.¹⁰ In particular, one must watch for signs of acute arterial occlusion in the lower extremities. Embolism from the aneurysmal sac or an atheromatous plaque can occur during aortic manipulation, and an embolectomy may be necessary on occasion.

Although it is generally agreed that the great majority of patients, even those with occlusive arterial disease, should undergo elective repair, there are some whom it is still prudent to exclude. Surgery on lesions above the renal arteries is quite hazardous. Patients with severe angina, congestive heart failure, or frequent episodes of cerebral ischemia are poor candidates because of a higher surgical mortality rate and a relatively high probability of dying of occlusive disease before aneurysmal rupture can occur. Aneurysms under 5 cm. rarely rupture before expanding further and are best left untouched if the patient has other significant cardiovascular disease. It should be pointed out, however, that an easily palpable aneurysm is usually greater than 5 cm.

Rupture of an abdominal aortic aneurysm is generally fatal, but some patients may be saved if they obtain prompt and competent care. An early leak may be temporarily tamponaded by retroperitoneal thrombus. The patient may develop excruciating back or abdominal pain and hypotension several hours before hemorrhage into the peritoneal cavity occurs. The sudden appearance of low back or abdominal pain in a patient with a palpable aneurysm warrants immediate laparotomy. In an obese patient over the age of 60, the constellation of severe pain and shock should suggest the strong possibility of a ruptured aneurysm even if none is palpable. If there is no electrocardiographic evidence of an acute myocardial infarction, surgical exploration should be performed immediately without awaiting radiologic procedures.

As long as the patient maintains a systolic blood pressure above 60 to 70 mm. Hg, it is probably not advisable to replete blood volume rapidly until the aorta has been clamped above the site of perforation because a higher perfusing pressure can cause dislodgement of the tamponading thrombus. After aortic clamping, prompt restoration of effective blood volume is essential, using the central venous pressure as a guide. Mannitol is given intravenously to induce diuresis and protect against renal failure. Arterial pH must be determined, and metabolic acidosis should be corrected with sodium bicarbonate. The postoperative course is often turbulent. Because of increased permeability of the inflamed mesentery and peritoneum, vast amounts of fluid may be sequestered retroperitoneally during the first 24 to 36 hours. Abrupt declines in circulating blood volume lead quickly to shock and oliguria. Blood pressure, central venous pressure and urine output must be monitored continuously as fluids are rapidly replaced. The appearance of acute renal failure may require dialysis (preferably hemodialysis) for several days. After the first 48 hours, the sequestered fluid begins to be reabsorbed, and the patient may develop congestive heart failure and sudden pulmonary edema if he has underlying heart disease. For this reason, prophylactic digitalization soon after surgery is often advisable. Adequate oxygenation is important at all times. The patient may require intermittent use of a respirator during the first few days because the large abdominal incision, the orthopneic position and the presence of shock lung syndrome may impede ventilation. If the patient survives the first 5 days with good cardiopulmonary and renal function, he is likely to recover, provided that wound dehiscence or retroperitoneal infection does not supervene.

Several other less common complications of abdominal aortic aneurysms deserve mention. Because of the large amount of mural thrombus in the sac, peripheral embolization can occur and result in acute femoropopliteal arterial occlusion or small infarcts on the feet. It is interesting to note that the high prevalence of peripheral arterial disease in patients with abdominal aortic aneurysms is due principally to femoropopliteal occlusion rather than aortoiliac obstruction.¹⁰ Perhaps recurrent silent emboli from the aneurysm contribute to the distal occlusive process.

A rare complication of arteriosclerotic aneurysms is bacterial infection, most commonly in aneurysms of the abdominal aorta. Only 35 cases of secondary infection of aneurysms have been reported,¹ but the incidence is probably higher than this sparsity suggests. In one autopsy study 6 of 178 arteriosclerotic aortic aneurysms were infected.¹⁹ *Salmonella* has been the most frequent offender (35 per cent of cases), followed by *Staphylococcus* (12 per cent). Patients generally present with fever of unknown origin or prolonged, intractable sepsis. Rupture has occurred in 79 per cent. Early surgical intervention, after institution of adequate antibiotic therapy, is necessary.

Finally a few cases of bleeding diathesis secondary to consumption coagulopathy have been reported in association with abdominal aortic aneurysms. Less severe forms will probably be detected in the future with the use of more sophisticated tests for fibrin split products.

ANEURYSMS OF PERIPHERAL ARTERIES

Peripheral artery aneurysms are much less likely to rupture but pose a greater threat to the viability of the involved extremities than aortic aneurysms (Table 2). The most frequent site is the popliteal artery. Popliteal aneurysms are almost always caused by arteriosclerosis, but post-stenotic dilatation probably increases the vulnerability of this vessel, since the aneurysm develops just distal to a point of compression (Hunter's canal or the arcuate popliteal ligament). Multiple aneurysms are generally present. In one series of 152 patients, 59 per cent of popliteal aneurysms were bilateral, 35 per cent were associated with abdominal aortic aneurysms, and 29 per cent were associated with femoral aneurysms.²¹ The diagnosis is easily made when the aneurysm is patent by palpating an expansile mass in the popliteal fossa, but a thrombosed aneurysm may be mistaken for a popliteal cyst. The diagnosis can be confirmed in about two thirds of cases with plain films of the area. Arteriography is usually unnecessary for diagnosis but it is helpful for planning surgery because it demonstrates the distal arterial run-off.

Complications of popliteal aneurysms can be divided into three categories: thromboembolism, compression, and rupture. Rupture occurs in less than 10 per cent of patent aneurysms and rarely in an occluded aneurysm.⁴ Venous compression often leads to edema and popliteal vein thrombosis, and sometimes pulmonary embolism. Local pain may develop as well as pain and paresthesias in the distribution of the posterior tibial nerve (posterior calf and heel).

The most serious local sequelae of popliteal aneurysms result from thromboembolism. Rapid or gradual thrombosis may occur in the aneurysmal sac, leading to either chronic arterial obstruction with intermittent claudication or acute ischemia with rest pain and gangrene. In some cases, transient loss of pulses may result from movement of thrombus in the aneurysmal sac. A hallmark of this lesion is showering of emboli into the tibial arteries and their branches, and one should think first of a popliteal aneurysm whenever a patient suffers repeated episodes of focal ischemia in a foot. In one series, 65 of 233 popliteal aneurysms had already been complicated by thrombosis and 23 by embolism at the time of initial diagnosis. In two other series, approximately two thirds of the affected limbs had impaired circulation.^{4, 8}

In considering therapy, one must take into account the natural history of popliteal aneurysms. Gifford and co-workers,¹¹ in reviewing 100 consecutive popliteal aneurysms in 69 patients, found that 49 had already been complicated by thrombosis, embolism, venous compression, or rupture at the time of initial diagnosis. In 70 cases managed conservatively, thromboembolism developed in 11, venous compression in 5, and rupture in 4 during a mean follow-up period of 44 months. Amputation was eventually required in 18. Of 45 patients with previously uncomplicated aneurysms, followed for an average of 46 months, complications developed in 13 (29 per cent), and 5 (11 per cent) had amputations. Twenty-four of the 32 aneurysms that remained uncomplicated were followed for less than 3 years. Wychulis et al.²¹ reported a 29 per cent complication

Table 2. *Aneurysms Distal to the Aorta*

LOCATION	USUAL ETIOLOGY	AGE AND SEX DISTRIBUTION	USUAL MODE OF PRESENTATION	COMPLICATIONS	INDICATIONS FOR SURGERY
Popliteal and femoral	Arteriosclerosis	Mostly males over 60	1. Pulsatile mass 2. Thromboembolism	1. Thromboembolism 2. Venous compression 3. Local expansion 4. Rupture occasionally	1. Patent lesions 2. Severe peripheral ischemia
Subclavian	1. Trauma of thoracic outlet syndrome 2. Arteriosclerosis	No predilection	1. Pulsatile mass 2. Thromboembolism	Thromboembolism	1. Patent lesions 2. Severe claudication
Splenic ²⁰	Idiopathic medial degeneration (more common with portal hypertension, splenomegaly, and multiparity)	Mostly females any age (mean in 50's)	1. Curvilinear calcification in left upper quadrant 2. Rarely palpable	Rupture in 6.6-9.2%	All lesions (excision with splenectomy)
Renal ³	Idiopathic	No sex predilection; mean age in 50's	1. Round calcification on x-ray 2. Hypertension (found on renal arteriogram)	1. Rupture in up to 15% (more likely in uncalsified lesions and during pregnancy) 2. Hypertension (probably due to renal thromboembolism) 3. Renal infarction	1. Large uncalsified lesions 2. Women in child-bearing age 3. Renal infarction
Superior mesenteric	Bacterial infection (e.g., bacterial endocarditis)	No predilection	Painful epigastric pulsatile mass in febrile patient	Rupture likely	All lesions

rate and 3 per cent amputation rate for a large series of initially asymptomatic aneurysms.

Because of this bleak outlook, surgical excision with replacement by a graft is recommended for all patients with patent popliteal aneurysms except those whose tolerance for anesthesia would be poor, and those whose life expectancy is severely limited. A review of three surgical series revealed only two operative deaths in 167 cases.^{1, 8, 21} Crichlow and Roberts¹ have reported patent distal vessels in 73 per cent and adequate circulation in 81 per cent of patients after a mean postoperative follow-up of 4.8 years, even though the majority of patients had circulatory impairment prior to surgery. Wychulis et al.²¹ reported good surgical results in 12 patients with asymptomatic aneurysms but an 11 per cent amputation rate for 64 aneurysms resected after serious thromboembolism had occurred. Most authors prefer autogenous saphenous vein grafts. Patients with chronically occluded popliteal aneurysms and intermittent claudication should be treated similarly to others with peripheral arterial occlusive disease.

Femoral aneurysms are the second most common peripheral aneurysms, and their clinical behavior is very similar to that of popliteal aneurysms. In one series of 89 patients thromboembolism occurred in 23, and 7 of 44 patients followed conservatively came to amputation.¹⁸ Femoral aneurysms are often in close proximity to iliac aneurysms, which have a high rupture rate. In these cases surgical repair is a greater problem because laparotomy is necessary in order to replace the entire iliofemoral segment.

Trauma may sometimes cause significant peripheral aneurysms. A good example is the subclavian artery aneurysm resulting from chronic compression in patients with thoracic outlet syndromes. This lesion is generally small but may thrombose or be a source of emboli to the hand. It should be considered in any patient with claudication of an upper extremity or digital artery occlusion. After arteriographic confirmation of the diagnosis, surgery should be directed at both the aneurysm and the offending structure in the thoracic outlet.

VISCERAL ANEURYSMS

The most common site for a visceral aneurysm is the splenic artery, followed by the renal arteries (perhaps 1 per cent of all aneurysms). Clinical characteristics are briefly outlined in Table 2.

SUMMARY

Aneurysmal dilatation of an artery is a common disease of the middle and later decades, often presenting clinically with catastrophic rupture, thromboembolism, or symptoms of compression. A major challenge of preventive medicine is the diagnosis of these lesions when they are still asymptomatic. This is only possible if careful attention to the arterial pul-

sations is paid during routine physical examination. Of particular importance is accurate palpation of the abdominal aorta, because an aneurysm in this region is highly lethal yet surgically reparable.

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Acute Respiratory Failure

Current Concepts of Pathophysiology and Management

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Interest in respiratory intensive care began in Scandinavia in the early 1940's, when it was realized that comatose patients with barbiturate poisoning could be managed with the lowest mortality rate by creating an artificial airway and using assisted ventilation until the drug was excreted and the patient regained consciousness. A few years later, in Europe and in the United States, epidemics of acute bulbar and spinal poliomyelitis served as another impetus to the development of interest in management of acute respiratory failure. Clinicians realized that death in the acute stage of poliomyelitis was usually a result of respiratory failure, and thus tracheostomy and the newly developed negative pressure "tank" respirators were utilized on hundreds of patients with that disease.

As the treatment procedure for barbiturate poisoning became routine, and as the incidence of poliomyelitis decreased nearly to the vanishing point in this country, interest in the management of acute respiratory failure began to lag. But in the 1950's a new disease—emphysema—began to be recognized in the United States, and large numbers of patients were hospitalized for treatment of the acute exacerbations that arose during the course of that disease. Arterial blood gas analysis soon became available to clinicians, and with it came the ability to diagnose and manage acute respiratory failure more rationally. At the same time positive pressure respirators were developed and were soon widely applied in the treatment of episodes of acute respiratory failure in these patients.

Interest in the problem of acute respiratory failure has greatly in-

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creased in the last decade, owing in large part to the almost routine use of arterial blood gas analysis in clinical practice. With its use has come recognition of the widespread prevalence of acute respiratory failure. As a result of its high mortality rate (over 20 per cent) and its many causes and complications, acute respiratory failure is today one of the most challenging therapeutic problems in acute medicine.^{5, 6} This review will briefly summarize the pathophysiology, causes, treatments, and complications of acute respiratory failure. For those interested in studying the subject in greater depth, two excellent textbooks are recommended.^{2, 10}

PATHOPHYSIOLOGY

The function of the lung is to assure adequate gas exchange so that aerobic metabolism may proceed normally. Normal gas exchange requires both normal total alveolar ventilation, and a satisfactory match-up of alveolar ventilation and capillary perfusion. The latter is known as the ventilation perfusion (V/Q) relationship. Acute respiratory failure develops clinically as a result of alveolar hypoventilation, or severe disturbance of the ventilation perfusion relationship, or both. Alveolar hypoventilation is the result of a generalized decrease in the total alveolar ventilation, and is characterized by hypoxemia, hypercapnia, and acidemia resulting from respiratory acidosis. Ventilation-perfusion abnormalities are due either to a localized or a diffuse but patchy decrease in the ventilation of still perfused alveoli, leading to shunting; depending upon their severity and extent, these abnormalities may lead to mild or very profound hypoxemia. Hypercapnia will, however, be an uncommon concomitant of V/Q problems, as they are more regional than generalized in the lungs. When hypoxemia itself becomes very severe, cellular hypoxia ensues, leading to anaerobic metabolism. This results in the production of large amounts of lactic and pyruvic acids, and a resulting acidemia from metabolic acidosis.

The presence of acute respiratory failure, its severity, and choice of therapy are all determined to a major degree from the arterial blood gas measurements. The importance of this procedure cannot be overemphasized; physicians should insist that this vital test be available in all hospitals.

Acute respiratory failure is usually defined as being present when the PaCO_2 is 50 mm. Hg or above, and/or the PaO_2 is 50 mm. Hg or below. When hypercapnia accompanies hypoxemia, acute respiratory failure is due to acute alveolar hypoventilation. When severe hypoxemia is present alone, it usually denotes a marked impairment of the V/Q relationship. Often, however, alveolar hypoventilation and V/Q abnormalities coexist in the same patients.

Acute respiratory failure may develop acutely in a patient with previously normal lungs, or as an acute illness superimposed on chronic disease of the lungs or chest wall. Chronic obstructive pulmonary disease (C.O.P.D.), the present designation for chronic bronchitis and emphysema, and such diseases as kyphoscoliosis and the Pickwickian syndrome of massive obesity, may all result in chronic alveolar

hypoventilation—and with it, chronic hypoxemia, hypercapnia, and compensated respiratory acidosis. Acute respiratory failure occurs in these diseases usually as a result of superimposed respiratory infection, which worsens blood gas abnormalities. Inadvertent use of sedatives, opiates, or excess oxygen therapy may also precipitate acute respiratory failure in patients with chronic alveolar hypoventilation.

ETIOLOGY

Normal lungs alone are not enough to maintain normal alveolar ventilation; an intact series of interconnected anatomic-physiologic “links” is also necessary. These links include: (1) the medullary respiratory center, (2) the neuromuscular connections from the respiratory center to the chest cage, (3) the bony bellows or chest cage itself, (4) patent airways, and (5) intact alveoli. Figure 1 illustrates the various diseases which may produce alveolar hypoventilation, and thus acute respiratory failure, by disturbing each of these five links.

In certain clinical states, alveolar hypoventilation results from a disturbance of more than one link in this chain. The best example of such a situation is the postoperative state. Following major surgery, especially

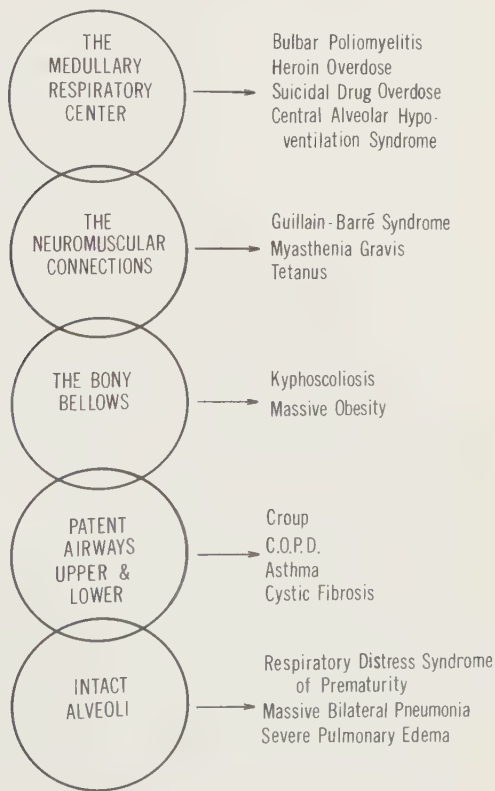


Figure 1. The interconnected anatomic-physiologic links that are necessary for maintenance of normal alveolar ventilation, and some diseases affecting them that can cause alveolar hypoventilation and acute respiratory failure.

in the upper abdomen, acute respiratory failure develops not uncommonly, and is one of the major causes of postoperative morbidity and mortality.⁹ The reason is clear if one examines the functional state of each of these five links during this important clinical period. The respiratory center is frequently depressed for several hours postoperatively owing to the premedications and anesthetic agents. The muscular component of the neuromuscular connections may be abnormal for some time after surgery if succinylcholine was used in combination with the anesthetic agents. After thoracic surgery the bellows are obviously abnormal, and after high abdominal surgery the pressure dressings and binders, coupled with diaphragmatic inflammation, greatly limit chest cage motion. Secretions become inspissated because of the low humidity of anesthetic gases, leading frequently to airway obstruction. Finally, alveoli often collapse because production of surfactant is impaired by various anesthetic agents.

In addition to alveolar hypoventilation, acute respiratory failure may result from severe ventilation-perfusion abnormalities. In these conditions hypoxemia predominates, the PaCO_2 is often normal, and acidemia, when present, is the result of the lacticidemic metabolic acidosis. Diseases producing this form of acute respiratory failure, frequently seen by surgeons, include fat embolism, "shock lung," and massive atelectasis.

Fat embolism, a well defined entity following extensive trauma, is characterized biochemically by the mobilization of various lipids into the circulation. One of the lipid components, the free fatty acids, exert a destructive effect on capillaries in the brain, skin, and lung. In the lung multiple areas of interalveolar hemorrhage develop, leading to decreased ventilation in areas still perfused and, therefore, hypoxemia.

Shock lung has been elucidated more recently.¹¹ It is seen in non-thoracic trauma and following hemorrhagic and endotoxin shock. The initial pathologic lesion is interstitial edema with some capillary thrombosis; later the intactness of the alveolar capillary membrane is disrupted, with red blood cells and plasma pouring into the alveoli in many areas. Again, as in fat embolism, the V/Q relationship is disturbed and hypoxemia results.

The "adult respiratory distress syndrome" ("stiff-lung syndrome") is certainly worthy of description. It produces acute respiratory failure by a combination of alveolar hypoventilation and a V/Q abnormality. Petty defined this group of diseases as having in common pathology which, in most instances, consisted of interstitial edema and interalveolar exudation.⁷ This syndrome, arising usually in patients with previously normal lungs, produces a very dangerous form of acute respiratory failure. Severe pulmonary edema, extensive bilateral viral and bacterial pneumonia, bilateral lung contusions following blunt chest trauma, and the severest cases of shock lung and fat embolism are among the causes. Clinically, the syndrome consists of progressive respiratory distress, extensive bilateral homogeneous shadows of consolidation on x-ray, increasing hypoxemia with difficulty in oxygenation even with increasing inspired oxygen concentrations, and progressive stiffening of the lungs requiring high respiratory pressures for adequate ventilation.

MANAGEMENT

Treatment of acute respiratory failure is much more effective when begun early. Once the diagnosis is established and treatment initiated, arterial blood samples should be analyzed often until they are normalized or stabilized, even if this takes many days. This practice, known as "monitoring," is performed by multiple arterial punctures or through the use of in-dwelling arterial cannulae.

The goal of treatment of any episode of acute respiratory failure in patients with previously healthy lungs is to attempt to normalize the disturbed gas exchange. In patients with acute exacerbations of chronic lung disease one should attempt no more than to return the arterial blood gas values to approximately what they were before the flare-up. It is obviously dangerous to fully oxygenate patients with chronic hypercapnia, as the loss of the hypoxic stimulus may lead to progressive respiratory center depression and worsening of the respiratory acidosis.

Treatment for acute respiratory failure falls, in general, into three categories:

(1) Specific therapy for underlying diseases which are the direct cause of the acute respiratory failure, such as opiate antagonists for heroin overdose, or antibiotics for extensive pneumonias; and treatment for medical problems which frequently coexist when acute respiratory failure is superimposed on chronic alveolar hypoventilation. Some examples are diuretics for right heart failure, phlebotomy for patients with hematocrits over 55 per cent, potassium chloride to prevent the frequent development of hypokalemic hypochloremic metabolic alkalosis, and antacids throughout the day to minimize the possibility of developing stress ulcers of the stomach and duodenum.

(2) "Conservative" techniques, useful alone in the management of mild acute respiratory failure. These include humidification, chest physiotherapy, and nasotracheal suctioning to help raise secretions, oxygen enrichment of the inhaled air, and aerosolized catecholamines such as isoproterenol for treatment of bronchospasm. These types of treatment may be administered at home in patients with chronic obstructive pulmonary disease and mild acute respiratory failure due to a superimposed respiratory infection, after the patient has had an initial arterial blood gas determination. They may also be all that is necessary in treating a hospitalized patient who develops mild to moderate acute respiratory failure postoperatively. These therapies may be administered in the patient's room and do not require his transfer to an intensive care unit. It must be emphasized that in patients with acute respiratory failure superimposed on chronic alveolar hypoventilation, supplemental oxygen must be administered only in controlled low concentrations. This can be done using either an oxygen analyzer to measure the inspired oxygen concentration, or through the use of the so called "venti-mask." The PaO_2 need rise only enough to terminate anaerobic metabolism without depressing the respiratory center. A PaO_2 of between 45 and 50 mm. Hg is usually satisfactory to achieve this goal.

(3) Use of a respiratory support system (RSS). This is reserved for pa-

tients with the severest acute respiratory failure. A respiratory support system is composed of a cuffed endotracheal tube, preferably oral; a respirator; an oxygen and a humidity source; easily removable and preferably disposable tubing connecting all the above; monitors with alarms to determine system malfunction; and apparatus for measuring minute ventilation and arterial blood gases.

Cuffed endotracheal tubes are strongly preferred over tracheostomy as the initial airway in almost all patients requiring a respiratory support system. Tracheal damage is no greater with a cuffed endotracheal tube than with a cuffed tracheostomy tube. In fact, the "high compliance cuff" now available should greatly decrease tracheal damage after the prolonged use of any intratracheal cuffed tube. Tracheostomy brings with it many difficulties; it is used as the initial airway only in patients with tetanus (because of the associated pharyngeal muscle spasm), in patients with facial burns or trauma which make an oral airway impossible to pass, and perhaps also in patients with severe chest trauma and a flail segment who will require prolonged ventilator treatment.

Indications for use of a respiratory support system are: (1) the comatose patient with severe acute respiratory failure; (2) patients with a PaO_2 under 40 mm. Hg who will not cooperate with the use of the "conservative" treatments mentioned above; (3) patients with acute respiratory failure who, even though cooperative, are unable to raise their PaO_2 over 40 mm. Hg while breathing 100 per cent oxygen; (4) patients with neuromuscular disease causing acute respiratory failure in whom the PaCO_2 has exceeded 50 mm. Hg; and (5) patients with severe blunt chest trauma with a flail segment, whose PaCO_2 is over 50 mm. Hg.

At this point a brief discussion is indicated concerning the types of respirators and the basis for their selection in any given patient. For greater detail the reader should refer to the two textbooks mentioned earlier,^{2,10} and to the article in this volume by Chusid and Bryan entitled "Application of Ventilators in Acute Respiratory Failure."

Basically the physician must make only two decisions concerning respirators. The first is whether the instrument should be set to "assist," in which case the patient will still initiate each respiration; or set to "control," in which case the respirator initiates each of a preset number of respirations per minute. "Assist" is used on conscious patients or comatose patients who have normal, regular, and vigorous breathing patterns. "Control" is used for patients, conscious or in a coma, who are breathing very slowly or irregularly because of respiratory center depression, or whose respiratory rate is extremely rapid: all these breathing patterns lead to severe gas exchange abnormalities. Bellows paralysis and chest trauma with a flail segment are the other common indications for the use of a respirator set to "control."

The second decision concerning respirators is whether a "pressure-limited" or "volume-limited" instrument is preferable. By and large, pressure-limited machines, which cycle off at a pre-set pressure, are satisfactory in patients with acute respiratory failure whose lungs are normal or only mildly diseased. "Volume-limited" ventilators, which cycle off after a preset volume has been delivered, should be used in the presence of severe airway obstruction or stiffness of the lung paren-

chyma owing to consolidation or edema, or when a rigid or traumatized chest wall is present.

Continuous positive pressure breathing (CPPB)—or PEEP, as it is also known (positive end-expiratory pressure)—was introduced by Petty several years ago for patients with intractable hypoxemia, usually as a part of a “stiff lung” syndrome, and represents a great therapeutic advance.¹ Adding positive end-expiratory pressure in very severely ill patients has frequently made possible satisfactory oxygenation—that is, a saturation of 88 per cent or above, using inspiratory oxygen concentrations of 60 per cent or less. There is not universal agreement as to whether oxygen toxicity is a real entity in human adults. However, those who accept the existence of oxygen toxicity feel that it will not occur even in patients receiving prolonged high concentration oxygen therapy if the inspired oxygen concentration is maintained at less than 60 per cent.

“Weaning” from a respirator may begin when the vital capacity, measured at the bedside using a special spirometer, is 10 cc. per kg. or greater. Weaning is carried out gradually. Time spent off the respirator is progressively increased, and arterial blood gases are measured to make certain that the patient is able to maintain adequate gas exchange in the absence of respiratory support. Extubation or removal of the tracheostomy is carried out when the vital capacity reaches 15 cc. per kg.

The 24 hours after extubation are crucial. Careful attention must be directed toward oxygenation, nasotracheal suctioning, and arterial blood gas monitoring during this period, for some patients may again develop acute respiratory failure following removal of the intra-tracheal airway, owing to retention of secretion and inadequate cough. This “post extubation syndrome” is dangerous but preventable.

One specific and extremely important form of acute respiratory failure must be commented upon. This is what we have come to call the “Syndrome of Acute Diffuse Bronchial Mucous Occlusion.” It is a complication of status asthmaticus which is responsible for the deaths of those 3 to 5 per cent of patients dying following hospitalization for acute asthma. In most patients with status asthmaticus, increasing dyspnea is due to increasing bronchospasm alone. In a minority, however, there is obstruction of the bronchi and bronchioles with thick tenacious mucus. Fortunately for the diagnosis of this syndrome, those patients with organic obstruction of the bronchial tree have a physiologic correlate of this abnormality in a rising PaCO_2 . Since most patients in status asthmaticus have a low to normal PaCO_2 , the presence of this syndrome is suggested when the PaCO_2 is 47 mm. Hg or above. Unless patients with organic bronchial obstruction complicating acute asthma are treated vigorously with more than conventional therapy, they may progress to severe acute respiratory failure with acute respiratory acidosis, become comatose, undergo cardiac arrest, and die.

The proper management of the hypercapnic asthmatic with this syndrome must include intrabronchial therapy as well as conventional treatments such as hydration, humidification, steroids, and bronchodilators. Nasotracheal suctioning should be employed every 15 minutes for 1 hour, and if the PaCO_2 has not decreased toward normal—or, indeed, has

continued to rise—the patient should then have bronchoscopy and lavage, under general anesthesia, or intubation and the use of a respiratory support system. Properly treated, patients with this syndrome usually have a normal PaCO_2 in 12 to 24 hours. We believe that death is totally preventable in these patients, and advocate the use of arterial blood gas measurement as an essential part of the evaluation of every patient with status asthmaticus.

Several published reports^{4, 8} have described the use of the membrane oxygenator and partial cardiopulmonary bypass in acute respiratory failure intractable to all other treatments. Although the device is currently being used in very few centers, its use should be considered in “stiff lung” syndromes where, following treatment with a respiratory support system including a volume ventilator, CPPB, and 100 per cent oxygen, the patient is still unable to raise the PaO_2 above 40 mm. Hg, and is growing weaker and stuporous. At the present time, however, the membrane oxygenator must be considered an experimental tool. Fortunately, since the introduction of CPPB, many patients with “stiff lung” syndromes formally considered to be intractable are now being adequately managed. However, as a device for potential future use, further investigation of the membrane oxygenator for short term therapy of acute respiratory failure should be encouraged.

COMPLICATIONS OF MANAGEMENT

Complications of management fall into two categories: problems related to the treatment of acute respiratory failure itself, and medical complications that often arise during the course of acute respiratory failure.

A still commonly encountered problem resulting from the treatment of acute respiratory failure is depression of the respiratory center owing to excessive oxygen administration. This is, happily, becoming somewhat less prevalent as physicians learn the importance of treating patients with controlled low concentrations of oxygen utilizing a venturi mask. The three most widely used of these specialized face masks deliver a predictable 24, 28, or 35 per cent oxygen to the inspired air, and one of these three concentrations is usually more than adequate to bring the PaO_2 and oxygen saturation to a level we consider satisfactory (that is, PaO_2 over 50 mm. Hg, and oxygen saturation in the low eighties). If, however, with low concentration oxygen therapy, the PaCO_2 rises more than 15 mm. Hg to achieve the desired PaO_2 and oxygen saturation, the patient should probably be intubated and placed on a respiratory support system.

In a patient on a respiratory support system, hourly minute ventilations must be measured with a spirometer. The adequacy of ventilation should also be doubly checked with an arterial blood gas measurement at least every 4 hours in the acutely ill patient. Leaks in the tubing component of the support system, obstruction in the endotracheal tube, secretions accumulating throughout the bronchial tree, and inadequate inspiratory pressure settings may all lead to decreased alveolar ventilation and increasing PaCO_2 during treatment. Most of these problems are eas-

ily discovered and corrected once it is recognized that the PaCO_2 is either rising or not falling satisfactorily.

Just as too little alveolar ventilation is bad, so also is too much alveolar ventilation. Dangerous alveolar hyperventilation occurs occasionally in patients on volume ventilators whose respiratory rates are being controlled. If this problem is not recognized early, patients may develop dangerous cardiac arrhythmias, seizures, and death when the pH rises significantly above 7.6. The importance of frequent measurements of minute ventilation and arterial blood gases in the patient with severe acute respiratory failure on a respiratory support system cannot be over-emphasized.

Stress ulcers of the stomach and duodenum, with hemorrhage, develop frequently in patients with severe acute respiratory failure. Bleeding may be massive, frequently leading to shock which is difficult to overcome even with large volumes of infused blood. If, in the first 12 to 16 hours after the onset of bleeding, the patient has several episodes of shock or remains in shock in spite of blood replacement, celiac axis angiography should be performed to find the bleeding site. This should probably be followed by surgery consisting of subtotal gastrectomy, bilateral vagotomy, and if one large bleeding area is present, ligation of its blood supply. Unfortunately, these patients sometimes develop acute renal failure as a result of their period of protracted hypotension; when severe, the acute renal failure requires peritoneal dialysis or hemodialysis. Mortality is, unfortunately, quite high in those patients with these multiple complications.

Cardiac arrhythmias are common complications of acute respiratory failure. They are considered to be due primarily to hypoxemia. In the patient receiving digitalis, they may also reflect toxicity to the drug, as the blood level of digitalis causing toxicity is significantly lowered in the presence of hypoxemia. Treatment consists of elimination of as much of the hypoxemia as possible, and then conventional treatment for each of the arrhythmias.

Atelectasis owing to an endotracheal tube slipping into the right lower lobe bronchus, pneumonia, and especially tension disorders including pneumomediastinum and pneumothorax are all occasional complications of the management of acute respiratory failure, and indicate the importance of daily chest x-rays in all such cases. In fact, any unexplained worsening of the arterial blood gas measurements, or any new symptoms developing in these patients, should alert the physician to obtain a new chest x-ray immediately.

Hospital-acquired pulmonary infections caused by gram-negative organisms, especially *Pseudomonas*, are very common, and probably result in part from contaminated respiratory therapy equipment, especially humidifiers. For this reason, the support system tubing and the humidifier water supply should be changed daily. Respiratory therapy equipment should be sterilized, and sterility carefully monitored by microbiologic surveillance of all respirators. Fever, new x-ray shadows, and two or more positive cultures of the same gram-negative organism in the sputum are evidence of a new hospital-acquired gram-negative pneumonia. Antibiotic therapy, usually with cephalothin and gentamicin, should be

started promptly. The danger of these gram-negative pneumonias stems from their frequent complication by septicemia, with endotoxin shock, disseminated intravascular coagulation, and later renal failure. Since hospital-acquired gram-negative infections are major complications of treatment for acute respiratory failure, and since gram-negative septicemia has a 50 per cent mortality, it is essential that everything possible be done to prevent occurrence of these infections.

A late complication of the management of acute respiratory failure that is being seen more commonly since the use of prolonged intra-tracheal tube treatment is tracheal stenosis. It appears several weeks to months following the removal of the tube and the patient's discharge, and usually occurs in patients whose cuffed endotracheal tube or cuffed tracheostomy was in place for 2 or more weeks. The pathogenesis of this tracheal injury seems to be pressure necrosis of the mucosa, submucosa, and tracheal cartilages by the cuff (balloon); healing is by fibrosis and scar formation, with ultimate stricturing.³ Symptoms of tracheal stenosis consist of increasing dyspnea and wheezing in a patient following hospitalization for acute respiratory failure. A loud wheeze is often heard on physical examination and the diagnosis is suggested by special physiologic studies and tracheal tomograms, which show a localized narrowing in the mid-zone of the trachea. The presence of this lesion is confirmed by bronchoscopy. Resection of the stenosis with end to end tracheal re-anastomosis, carried out by a surgeon experienced in this operation, achieves excellent results with very low mortality.

EXPERIENCE WITH THE MANAGEMENT OF ACUTE RESPIRATORY FAILURE

In October of 1968 the Respiratory Intensive Care Unit of the Division of Pulmonary Medicine was officially constituted in one geographical area of the Queens Hospital Center. Occasional cases of acute respiratory failure had been treated prior to that time in a number of different rooms on the same floor. A registry of acute respiratory failure was also established. It includes all patients treated in the respiratory intensive care unit, with special emphasis in the registry given to those patients whose PaCO_2 was over 50 mm Hg. The registry contains diagnoses, complications, and mortality figures. Not all patients at this institution with acute respiratory failure were treated in this unit; those treated on various medical and surgical floors are not included in the data to be described below. Table 1 describes a comparison of two different periods. The first is a 21 month period beginning prior to and ending 16 months after patients began to be treated in this specialized unit. The second is a 16 month period summarizing our recent experience from July 1971 to October 1972.

Several facts emerge. First, the volume of patients treated greatly increased as the Respiratory Intensive Care Unit became known and trusted in this medical center and the surrounding community. (In fact, the patients listed for the second period represent only 57 per cent of the total patient volume during this time; the other 43 per cent also had acute

Table 1. *A Comparison of Causes and Mortality in Hypercapnic Patients with Acute Respiratory Failure Treated in the Respiratory Intensive Care Unit of Queens Hospital Center*

MAY 1968 TO FEBRUARY 1970 — 21 MONTHS			JULY 1971 TO OCTOBER 1972 — 16 MONTHS		
	NO. OF PATIENTS	NO. OF DEATHS		NO. OF PATIENTS	NO. OF DEATHS
Chronic obstructive pulmonary disease	84	27	Chronic obstructive pulmonary disease	72	16
Old thoracoplasty	2	2	Asthma	42	2
Drug overdose	1	—	Drug overdose	10	1
Post abdominal surgery	3	—	Bacterial pneumonia	4	2
Diffuse interstitial fibrosis	2	—	Diffuse interstitial fibrosis	3	1
Kyphoscoliosis	3	2	Crushed chest	4	2
Muscular dystrophy	1	—	Respiratory burns	3	1
Total	96	31	Tetanus	1	1
Mortality rate—32 per cent			Guillain-Barré syndrome	2	2
			Varicella pneumonia	1	1
			High airway obstruction	4	1
			Bronchiolitis	3	1
			Pickwickian syndrome	2	—
			Tuberculosis with hemoptysis	3	1
			Hypokalemia paralysis	1	—
			Diffuse pulmonary		
			Hodgkin's disease	2	—
			Total	157	32
			Mortality rate—20 per cent		

respiratory failure but were not included as their PaCO_2 was less than 50 mm. Hg. The second fact of interest is the variety of diagnoses noted. Many different disease processes are now being treated in children and adults, covering all areas of medicine. Third and most striking was the fall in mortality. The fall from 32 to 20 per cent reflects the growing experience of the staff.

Thus, when our respiratory intensive care unit was first established, it handled a limited patient volume and a limited number of diagnoses (usually acute exacerbations of chronic respiratory diseases). The patients remained in the unit for a rather prolonged period, and the mortality was approximately one-third. As the years passed, more cases of more varied etiologies and of all age groups (except neonates) were referred; and both duration of stay and mortality decreased.

We are convinced that respiratory intensive care, administered in specialized units, makes an excellent contribution to the improvement of patient care, the training of physicians, and the teaching of students in medicine, nursing, and respiratory therapy.

CONCLUSION

The widespread use of arterial blood gas analysis in acute medicine has led to an appreciation of the prevalence and danger of acute respira-

tory failure. It is essential that education of physicians and allied health professionals in this area continue, so that mortality from acute respiratory failure may be minimized. It is hoped that acceptance by physicians of the vital role of professionally trained respiratory therapists will be rapid. Respiratory intensive care units are being developed in many hospitals; through their use, coupled with modern methods of transportation for sick patients, we may yet see regionalization of health care delivery for the sickest patients with acute respiratory failure. Goals for the near future include computerized bedside monitoring of patients who are on a respiratory support system; lessening of the risk of hospital-acquired infections in these patients; and development of an efficient and safe artificial lung to tide patients over the most severe episodes of acute respiratory failure.

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Application of Ventilators in Acute Respiratory Failure

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Pulmonary insufficiency implies a failure of the lung to accomplish one or both of its two major functions—that is, inability to oxygenate the capillary bed to maintain an acceptable arterial Po_2 (respiratory failure), and inability to maintain an acceptable arterial Pco_2 and pH by failure to ventilate the alveoli adequately (ventilatory failure). In either instance of insufficiency, a mechanical ventilator may be required to maintain a body milieu sufficient to prevent tissue death. Mechanical ventilation may be necessary to prevent hypoxemia alone, hypercapnia not being present, or may be necessary to treat apnea and/or hypercapnia with acidosis, hypoxemia being the lesser problem to control.

When mechanical ventilation is necessary to treat hypoxemia, it is due to the fact that either the oxygen cannot be delivered to the patient without danger of progressive hypercapnia and coma developing, or the hypoxemia is of such severity that an acceptable arterial Po_2 (60 mm. Hg) cannot be maintained by the use of ordinary oxygen devices such as nasal cannulae, catheters, or masks. In the latter circumstance, intubation is required to administer controlled oxygen concentration during mechanical ventilation. Intubation is also usually required to treat hypercapnia by mechanical ventilators since satisfactory adjustments of tidal volumes and minute ventilation must be achieved.

The selection of the ventilator to be used is based on the clinical condition causing hypoxemia and/or hypercapnia, the individual characteristics of the ventilator, and whether the patient needs respiratory assistance, control, or a combination of both.

SITUATIONS REQUIRING MECHANICAL VENTILATION

In a representative 6 month period at the Mount Sinai City Hospital Center at Elmhurst, 219 patients with acute pulmonary insufficiency

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Table 1. *Indications for Mechanical Ventilation, and Preferred Ventilator in 219 Patients*

CLINICAL INDICATION FOR MECHANICAL VENTILATION	VENTILATOR OF CHOICE
1. Sedative or narcotic overdose with respiratory suppression (26)	Volume-cycled ventilator
2. Apnea with or without shock (11)	Volume-cycled ventilator
3. Adult respiratory distress syndrome (40)	Volume-cycled ventilator
4. Neonatal respiratory distress syndrome (1)	Volume-cycled ventilator
5. Flail chest (crush chest) (3)	Volume-cycled ventilator
6. Pickwickian syndrome (1)	Volume-cycled ventilator
7. Chronic obstructive pulmonary disease (67)	
a. Alert with or without hypercapnia	Pressure-cycled ventilator
b. With respiratory acidosis	Volume-cycled ventilator
8. Chest wall and spinal disease (1)	Volume-cycled ventilator
9. Asthma (36)	
a. Without respiratory acidosis	Pressure-cycled ventilator
b. With respiratory acidosis	Volume-cycled ventilator
10. Congestive heart failure with respiratory acidosis (16)	Pressure-cycled ventilator
11. Polyneuropathy, myopathy (17)	Pressure-cycled and volume-cycled ventilators

required mechanical ventilation. Not included are patients using ventilators for routine aerosol or humidification treatments. There were 119 males and 100 females, ranging in age from 7 to 90 years old. Table 1 designates the clinical conditions necessitating mechanical ventilation and the preferred ventilator in each instance. This list of conditions is comparable to reports from other institutions employing the same type of therapy.⁸

It may be seen that not all the conditions are primary lung diseases; respiratory center depressions, chest cage ailments, neuromuscular diseases, circulatory defects, and obesity problems may also cause hypoxemia and hypercapnia. As indicated in Table 1, in most cases respiratory control was achieved with volume-cycled machines, the pressure-cycled machines being employed mainly for assisting ventilation in alert patients receiving oxygen, or intermittently for administering aerosols for bronchodilation or expectoration of sputum.

Intubation was employed in 75 per cent of the 219 patients, the average number of days on a ventilator being 5 to 6 days. Nasotracheal intubation was the intubation procedure most often selected, with only 6.8 per cent of patients requiring tracheostomy. Nasal or oral intubation should virtually always be attempted in carrying a patient through his crisis, without having to resort to a tracheostomy.

CHARACTERISTICS OF VENTILATORS AND TERMINOLOGY

The usual classification of ventilators includes pressure-cycled, volume-cycled, and time-cycled types.¹ Table 2 indicates the available venti-

Table 2. *Classes of Ventilators with Examples of Each*

Pressure-cycled	Volume-cycled
Bennett	Air-Shields
Bird	Bennett MA-1
Cof-Flator	Drager
Exsufflator	Emerson
Fluidic Retec	Engstrom
Hand-E-Vent	Ohio 560
Monaghan	
MSA	Time-cycled
Pulmo-Vent	Mörch
Wilson	Cuirass Type (Emerson, Monaghan)

lators in each class, the list not being totally inclusive since the development of these machines is proceeding at such a rapid pace. The volume-cycled group always requires intubation,⁸ since the tidal volume and minute ventilation settings call for non-leak airway conditions.

Pressure-cycled ventilators deliver a gas at an adjustable pressure, with the resultant tidal volume dependent upon the airway flow characteristics and lung compliance. Volume-cycled ventilators deliver a preset volume of gas at whatever pressure is needed, according to the physical characteristics of the airways and lungs. These capabilities of each mean that the pressure-cycled machines achieve only relatively low peak pressures and have limited flow mechanics above 40 cm. cycling pressures.¹ Thus, the tidal volume of pressure-cycled machines varies as pulmonary resistance varies. Furthermore, unless an oxygen blender or electronic monitoring device is used for measuring oxygen concentration, the inspired oxygen cannot be controlled accurately with a pressure-cycled machine. The volume-cycled ventilators deliver constant volumes against changing resistance, have the ability to accurately control inspired oxygen concentrations, and have the ability to alter inspiratory-expiratory ratios for a greater patient adaptation.

Several terms have now come into use in regard to pressures at end-expiration and during the cycling of a mechanical ventilator. Table 3 defines these terms and indicates how the pressures are achieved. PEEP is particularly useful in hypoxemia when the arterial P_{O_2} cannot be raised to an acceptable level. This applies mainly to the adult respiratory distress syndrome,⁶ or the neonatal respiratory distress syndrome.⁴ Several volume-cycled ventilators have built-in devices for creating this effect at end-expiration. If the device is not available, positive pressure may be achieved on either a pressure-cycled or volume-cycled machine by leading the expiratory tubing under water in a sealed bottle.¹⁰ The mechanism by which PEEP accomplishes better oxygenation has been described elsewhere.⁵ By its application, a lower inspired oxygen concentration (FIO_2) may be achieved and oxygen toxicity hopefully avoided.

INPB (with NEEP) should be used only by experienced personnel, and in selected situations where inspissated mucus must be cleaned

⁸The Mörch ventilator may function as a volume ventilator.

Table 3. *Definitions of Ventilator Terms*

ABBREVIATION	MEANING	HOW ACHIEVED
1. IPPB	Intermittent positive pressure breathing	Inspiratory positive pressure using pressure-cycled machine for brief periods
2. IPPV	Intermittent positive pressure ventilation	Inspiratory positive pressure using pressure-cycled machine continuously for ventilation
3. INPB	Intermittent negative pressure breathing	Expiratory negative pressure using pressure-cycled machine
4. CPPB	Continuous positive pressure breathing	Positive pressure applied by mask in both inspiration and expiration
5. CPPV*	Continuous positive pressure ventilation	Positive pressure applied by ventilator in both inspiration and expiration
6. PEEP*	Positive end expiratory pressure	Positive pressure of 1 to 15 cm. H ₂ O achieved by ventilator at end expiration
7. PEPP	Positive expiratory pressure plateau	Positive pressure of 1 to 15 cm. H ₂ O achieved by ventilator at end expiration
8. CPAP*	Continuous positive airway pressure	Positive pressure applied by ventilator both in inspiration and expiration
9. NEEP	Negative end expiratory pressure	End expiratory pressure of -1 to -100 cm. H ₂ O achieved by ventilator
10. ZEEP	Zero end expiratory pressure	Baseline end expiratory pressure of 0 cm. H ₂ O achieved by allowing passive expiration

*May be used interchangeably.

from otherwise "normal" lungs, since there is a danger of rapid alveolar collapse, and sudden increases that may occur in pulmonary perfusion.

MANIPULATION OF VENTILATORS AND MONITORING TECHNIQUES

The adjustment of a ventilator requires recognition of the complete clinical and metabolic condition of the patient and knowledge of the characteristics of the machine. A baseline arterial analysis is absolutely essential to determine the starting point for treatment of hypercapnia and acidosis and/or hypoxemia. The arterial P_{CO_2} level does not have the same import as the pH level since patient consciousness varies with acute versus chronic hypercapnia. However, when the pH falls below 7.30 with hypercapnia present, ventilation is required. The total volumes to be achieved are governed by the ventilatory changes of P_{CO_2} and pH, but the initial setting of tidal volume may be obtained from standard calculations such as the Radford nomogram.⁷ When calculating tidal volumes on volume-cycled machines, the compliance factor of the ventilator must be accounted for, thus causing a reduction of actual volume delivered by 50 to 100 cc.

A discussion of each ventilator setting is beyond the scope of this report; specific ventilators are adequately discussed in available booklets and references.² Monitoring techniques are essential for serial observation and prevention of complications. Data used in following patients on mechanical ventilation are shown in Table 4. The FIO_2 selected should be

Table 4. *Data for Monitoring Patients During Controlled Mechanical Ventilation*

ABBREVIATION	DEFINITION
FIO ₂	Inspired oxygen concentration (%)
FEO ₂	Expired oxygen concentration (%)
PIO ₂	Partial pressure of inspired oxygen (mm. Hg)
PECO ₂	Partial pressure of expired carbon dioxide (mm. Hg)
PaO ₂	Arterial oxygen tension (mm. Hg)
PaCO ₂	Arterial carbon dioxide tension (mm. Hg)
pH	Acid-base status
TV	Tidal volume (liters)
IP	Inspiratory pressure (cm. H ₂ O)
TV/IP	Compliance of patient (liters/cm. H ₂ O)
PIO ₂ -PaO ₂	Inspired oxygen/arterial oxygen gradient (difference in mm. Hg)
CVP	Central venous pressure (cm. H ₂ O)

the lowest necessary to keep the PaO₂ at 60 mm. Hg or more, that is, below 40 to 50 per cent levels. The arterial pH should be observed carefully since alkalosis induced by rapid reductions in PaCO₂ may lead to cerebral instability and/or cardiac arrhythmias. The compliance of the patient should preferably stay stable or increase, that is, the inspiratory pressure readings should stay the same or become lower as long as tidal volume settings are constant. If compliance is reduced (increasing IP readings), one of several factors may be the cause: airway obstruction, pulmonary edema, hydration overload, oxygen toxicity, atelectasis as a result of loss of surfactant from persistent ventilation, or congestive failure. The PIO₂-PaO₂ (alveolar-arterial) gradient should show gradual reduction, a progressive rise indicating diffusion barriers developing within the lung.

If sophisticated equipment is not available for monitoring, the minimum of data for following a patient on mechanical ventilation includes blood pressure (to detect hypotension from increased thoracic pressure impeding pulmonary perfusion), central venous pressure (to detect early changes from thoracic pressure changes), compliance (calculated from ventilatory readings of TV and IP), EKG (to detect arrhythmias from pH changes), and arterial gases with pH. The arterial Po₂ should be maintained between 60 and 100 mm Hg, and the arterial Pco₂ at the level at which the pH is compensated between 7.35 and 7.45.

HAZARDS OF MECHANICAL VENTILATION IN ACUTE SITUATIONS

Respiratory alkalosis is one of the most common complications of manipulating ventilation with a mechanical ventilator, especially when volume-cycled machines are used. The pH should be carefully observed, since many pulmonary patients have underlying metabolic alkalosis from the use of diuretics and corticosteroids. A rapid reduction in arterial Pco₂

by ventilation may produce a combined metabolic and respiratory alkalosis, leading to extreme cerebral and muscular irritability. Coincident with the use of diuretics and corticosteroids is hypokalemia. Patients on digitalis therapy receiving mechanical ventilation are prone to develop cardiac arrhythmias, and for this reason potassium chloride should be administered, even prophylactically, to ward off the complication. In the 219 patients comprising this report, 40 patients (18 per cent) developed cardiac irritability necessitating treatment.

The ventilator lung syndrome (stiff lung) may occur for a variety of reasons.^{3,9} Among these are: persistent ventilation at constant nonchanging tidal volumes with loss of surfactant, oxygen toxicity using an FIO_2 of more than 50 per cent, overhydration from humidification, and overperfusion from a combination of parenteral fluids and inappropriate secretion of antidiuretic hormone. To avoid some of these problems, a sighing mechanism should be utilized several times an hour, and the total fluid requirement of the patient should include the combination of humidifying liquids and parenteral fluids. Manual bagging with frequent suctioning is advisable.

Formerly a common complication, transmissible infection is fortunately becoming less so. The patient may become infected by transference of machine parts from one person to another, or may become contaminated by the water residue in the humidifying apparatus. Infection by these routes may be avoided by changing the machine tubing every 24 hours. Cultures should be obtained every 48 hours from the site of intubation, the ventilator tube entries, and all sites of water emission from the humidifying system.

Pressures obtained by volume-cycled ventilators may reach peak levels (60 to 100 cm. H_2O); and occasionally lung blow-outs occur. Pressures should be maintained below 50 to 60 cm. H_2O , since bilateral pneumothorax can be fatal. Pertinent in this respect are pressures attained when using PEEP. Inspiratory pressures will rise considerably when applying expiratory positive pressure, and inspiratory pressure alarm systems should be appropriately adjusted.

FAILURE OF VENTILATOR TO ACHIEVE DESIRED RESULT

Sudden death, shock, hemorrhage, or other such events may occur during mechanical ventilation. Twenty-six patients (12 per cent) had an acute catastrophic episode during therapeutic trials of mechanical ventilation, at times when it appeared that they were improving. Patients with severe emphysema, bullous emphysema, protracted hypercapnia, and pulmonary hypertension are among the most difficult to stabilize. Patients with arteriosclerotic heart disease are vulnerable to further ischemia and infarctions from arrhythmias and fluid changes. Pulmonary embolization may occur because of prolonged bed rest, and this should be considered in cases of prolonged hypoxemia, heart failure, and arrhythmias. Aspiration pneumonia may occur at any time, and skilled suctioning and manipulation of endotracheal balloons is important. Chest films should be obtained frequently and observed serially.

Early selection of the proper ventilator is imperative. All too often "a child is called upon to do a man's work" and pressure-cycled ventilators are selected because of ease of manipulation. In many situations, pressure-cycled ventilators do not efficiently increase minute volume, despite an alteration in respiratory rate. What actually may be happening is an increase in metabolic rate and an increase in dead-space ventilation, with resultant further hypercapnia.¹¹ In 34 patients, a transfer to a volume-cycled ventilator was required before the desired result was achieved.

Finally, inexperienced personnel may change ventilator settings. Therefore, the preferred location for the treatment of acute pulmonary insufficiency is in a designated area (ICU or RCU), where attending physicians, house staff, nurses, and therapists have the required skill.

SUMMARY

A review of the use of mechanical ventilation in 219 selected patients with various causes of acute pulmonary insufficiency has been presented. The choice of ventilator depends on the clinical condition of the patient and the individual characteristics of the ventilator. Careful monitoring techniques are imperative in order to avoid overtreatment and physiologic hazards. The ideal location for the use of mechanical ventilators and treatment of acute pulmonary insufficiency is in a designated area for pulmonary intensive care.

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Medical Conditions Mimicking the Acute Surgical Abdomen

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A significant number of patients presenting with acute abdominal pain suffer from nonsurgical conditions. Failure by the examining physician to recognize important clinical clues may lead to unwarranted and often harmful surgical intervention. Since complete reviews of the differential diagnosis of the acute abdomen can be found elsewhere,^{6, 14, 15} this discussion will be limited to those clinical signposts which should alert the clinician to a possible medical etiology, together with a review of those conditions commonly accompanied by acute abdominal symptoms (Table 1).

DIAGNOSTIC SIGNPOSTS IN HISTORY

PRESENT HISTORY. Although a complete description of the patient's abdominal symptoms should be obtained, this alone is seldom helpful in identifying a medical cause. Attention should be paid to events surrounding the onset of pain, including possible relationship to physical exertion, use of drugs, or time of menses. Factors affecting the pain, such as respiration or position, should be noted, as should extra-abdominal (shoulder or testicular) radiation. Even greater attention should be given to systemic features accompanying the abdominal complaints. Unusually high fever, chills, or profuse diarrhea should alert the physician to a possible medical condition. Active joint symptoms occurring with an acute abdomen, or skin eruptions appearing at the onset of symptoms, should cast immediate doubt on a surgical diagnosis. Other clinical features which should arouse suspicions of a nonsurgical condition include unexplained dyspnea, pleuritic chest pain, urethral or vaginal discharge, bloody or unusually dark urine, and concurrent neurological symptoms.

PAST HISTORY. A history of similar recurring episodes of acute abdominal distress, often dating back to childhood, suggests a medical diagnosis. This is especially true if there is a family history of such occur-

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Table 1. *Medical Conditions Causing the Acute Abdomen*

	FAMILIAL METABOLIC
Acute intermittent porphyria	Hereditary angioneurotic edema
Familial hyperlipoproteinemia	Hemochromatosis
Familial mediterranean fever	
	ENDOCRINE
Diabetic ketoacidosis	Hyperthyroidism
Addisonian crises	? Hyperparathyroidism
	INFLAMMATORY
<i>Noninfectious</i>	
Pancreatitis	
Inflammatory bowel disease	
<i>Infectious</i>	
Enteric infections (typhoid, shigellosis, staphylococcal enterocolitis, etc.)	Infectious mononucleosis
Primary peritonitis (pneumococcal, tuberculosis)	Herpes zoster
Pelvic inflammatory disease	Pyelonephritis
Hepatitis (viral, Q fever, alcoholic)	Prostatitis
	Nonspecific jejunitis (?)
	Mesenteric adenitis (?)
	REFERRED PAIN
Thoracic	Neurologic
Pericarditis	Tabes dorsalis
Pleuritis	Nerve root compression
Acute myocardial infarction	Glaucoma
Myocarditis	Pelvic
Abdominal wall (rectus sheath hematoma)	Mittelschmerz
Retroperitoneal	Endometriosis
Renal colic	Abdominal migraine
Renal infarction	Abdominal epilepsy
	COLLAGEN HYPERSENSITIVITY
Acute rheumatic fever	Henoch-Schoenlein purpura
Systemic lupus erythematosus	Allergy (?)
Polyarteritis nodosa	
	DRUG-TOXIN
Heavy metals (lead, arsenic, mercury)	Arachnoidism
Mushroom	Anticoagulants (especially coumadin)
Staphylococcus toxin	Narcotic withdrawal
	HEMATOLOGIC
Sickle cell anemia	Leukemia
Acute hemolytic states	Clotting abnormalities

rences. A patient with a history of recurrent joint, pleuritic, or unusual dermatologic complaints should also be approached with this in mind. One should always be wary of the older patient with a strong history of coronary disease, especially increasing angina. An often overlooked clue is a past history of passing renal calculi or gravel. A detailed inquiry into possible drug ingestion must not be neglected since a number of acute abdominal manifestations are caused by drug use. Finally, the physician should be alert to a suspicious occupational history or a history of recent extensive travel.

SPECIFIC SIGNPOSTS IN PHYSICAL EXAMINATION

In examining the patient with an acute abdominal complaint for a possible medical condition, careful search should be made for purpuric or other skin eruptions (especially painful or nodular lesions) and evidence of active joint inflammation. Other findings suggestive of a medical condition include extensive adenopathy, friction rubs, unusual hepatomegaly, splenomegaly, and gross neurological deficits. When abdominal findings are minimal, but the patient's distress is severe, the physician should consider a medical condition as cause of the pain — particularly if the patient is young.

REPRESENTATIVE CONDITIONS ACCOMPANIED BY ACUTE ABDOMINAL PAIN

FAMILIAL METABOLIC DISORDERS

Acute Intermittent Porphyria

Although presumably inherited as an autosomal dominant trait, this disorder appears to affect females more commonly.¹⁹ It is characterized by recurrent episodes of colicky abdominal pain frequently associated with major neurologic manifestations. A careful review will reveal passage of dark urine in three fourths of these patients, recent ingestion of barbiturates in one third, and a relationship between colicky abdominal pain and menses in some women. The most common findings include a normal temperature, tachycardia, hypertension, and postural hypotension. Abdominal examination is generally unremarkable and hepatomegaly is virtually never present.

In the majority of patients pain will be accompanied by significant neurologic deficits. Hallucinations or mental confusion are most common, but motor weakness (especially quadriparesis) may be prominent, as may abnormalities in cranial nerves and deep tendon reflexes. While profound hyponatremia and high protein-bound iodine and cholesterol are seen occasionally, the specific diagnosis is made by detection of elevated levels of urinary porphobilinogens and other porphyrin precursors.

Familial Hyperlipoproteinemia

This diagnosis is usually established by the discovery of a deeply lactescent serum in a patient with recurrent abdominal pain.⁸ The rare type I pattern invariably appears in early childhood with the clinical picture of recurrent, severe abdominal crises associated with eruptive xanthomas, hepatosplenomegaly, and lipemia retinalis. Diagnostic are marked elevations of serum chylomicrons induced by exogenous fat, and low post-heparin lipolytic activity. Type V hyperlipoproteinemia, which usually appears during the second or third decade, presents with a similar clinical picture, though hepatosplenomegaly is a less constant feature. The close association of this lipid disorder with certain cases of acute pancreatitis has been receiving increasing emphasis.³ In some cases it appears that the lipid defect occurs secondary to an attack of acute pancreatitis,³ while in other instances the lipid defect is the primary event initiating the episode. Recently estrogen therapy has been shown to result in the appearance of an overt type V pattern, triggering acute pancreatitis in patients later shown to have the occult familial form of this lipid disorder.⁹

The type V pattern is characterized by marked elevations in both triglyceride and chylomicron fractions, with a high pre-beta lipoprotein on lipid electrophoresis.⁸ Abnormal carbohydrate tolerance is also generally present.

Familial Mediterranean Fever

This diagnosis should be suspected in any patient of Mediterranean ancestry with a history of recurrent episodes of polyserositis and acute abdominal pain.¹⁸ Typically, patients present with acute abdominal distress and clinical findings of peritonitis. Pleuritis may be present and a small pleural effusion can often be detected by x-ray. Three fourths of patients will have joint involvement, generally monarticular, at some time; there is a predilection for larger joints, especially knees, ankles, or hips. An erysipelas-like erythema, usually of the legs, is not uncommon. Splenomegaly is frequently noted. Individual attacks of serositis may involve one organ system or several concurrently. Amyloidosis will develop in about one fourth of patients, with renal involvement ultimately leading to a fatal uremia. Proteinuria is usually the earliest evidence of this complication. There are no diagnostic laboratory features of this disorder although a few cases have been reported with elevated etiocholanolone levels.

Hereditary Angioneurotic Edema

This is a rare hereditary disease transmitted as an autosomal dominant and characterized by intermittent episodes of abdominal pain, localized, non-inflammatory edema, and serious laryngeal edema.⁷ The nonspecific abdominal pain may be accompanied by loose bowel movements and minimal abdominal tenderness. A small amount of peritoneal fluid, clinically inapparent, may be found on paracentesis. Barium study of the upper, and occasionally lower, gastrointestinal tract will show typical features of submucosal edema. A low level of complement-1-esterase (C-1) inhibitor is a consistent biochemical feature of this disorder.

ENDOCRINE DISORDERS

Hyperthyroidism, Addisonian crisis, and rarely hyperparathyroidism (without pancreatitis) may all present as acute abdominal pain. This unusual presentation should be accompanied by more specific features of the endocrine disorder, making the diagnosis obvious. Certainly the diagnosis of acute adrenal insufficiency should be considered in patients with acute abdominal distress who have previously received long-term steroid therapy.

Abdominal pain and vomiting are common in diabetic ketoacidosis and on occasion may be severe enough to simulate an acute abdomen. A past history of diabetes, recent onset of polyuria or polydipsia, and characteristic Kussmaul respirations in a severely dehydrated patient usually make the diagnosis of diabetic ketoacidosis obvious. The presence of glycosuria and acetonuria should immediately call attention to this possibility, if it was not suspected initially. Occasionally there is an associated pancreatitis, which should be considered in the patient with more than minimal abdominal signs.

NONINFECTIOUS INFLAMMATORY DISORDERS

Pancreatitis

This is unquestionably the most important medical cause of acute abdominal pain leading to unnecessary surgery. Pain which may begin gradually or quite abruptly, has a persistent boring quality, often penetrating to the back and intensifying in the supine position. It is most commonly located in the mid-epigastrium but may radiate to any region of the abdomen. On physical examination epigastric tenderness is usually present, but board-like rigidity is unusual. In fact, physical findings may be quite minimal. Left flank tenderness is common and may even suggest a renal etiology. Abdominal distention and mild ileus are frequently seen. Periumbilical bluish discoloration (Cullen's sign) or left flank ecchymosis (Grey-Turner's sign) are seen only in the hemorrhagic form, and then infrequently. In rare instances nodular, red, tender areas of subcutaneous fat necrosis may appear on the extremities or trunk—or even in the periarticular areas, mimicking arthritis.

In about 10 per cent of cases a chest x-ray will show the presence of a small pleural effusion, generally on the left. A flat plate of the abdomen may show calcifications in the region of the pancreas or a solitary air-filled loop of jejunum in the same area, the so-called "sentinel-loop." Less often an air-filled right and transverse colon may be seen with absence of air in the left colon, presumably because of the inflammatory process extending to the splenic flexure area from the adjacent pancreas.

The most helpful laboratory finding present in most cases is an elevated serum amylase concentration. The rise may be extremely transient, sometimes lasting less than 24 hours. In this circumstance a serum lipase may then prove useful since it usually remains elevated for a longer time.

Since renal clearance of amylase increases in pancreatitis, urinary amylase values may be elevated even when serum levels are equivocal. Measurement of total urinary amylase excretion per hour, rather than concentration, using timed 2 hour samples has been shown to yield the most meaningful information.

Of more immediate concern to the clinician is the problem of distinguishing pancreatitis from certain surgical conditions²⁰ associated with elevated amylase levels, including perforated viscus, mesenteric infarction, ruptured ectopic pregnancy, or even ruptured aortic aneurysm. In these circumstances the actual level of serum amylase will have only relative discriminative value and other clinical data must be relied upon. As a general rule, serum amylase levels tend to be less than 500 Somogyi units in acute surgical conditions, while in pancreatitis they range from 200 to 1000 units. Interestingly, the serum amylase concentration in acute pancreatitis often varies inversely with the severity of the illness.¹ Values over 1000 units for the most part reflect a nonacute surgical condition, principally biliary tract disease with edematous pancreatitis.¹ If a pleural effusion is present, measurement of amylase content of the effusion may be diagnostic, since values substantially greater than those of serum are found almost exclusively in pancreatitis (aside from rare cases of esophageal rupture) or lung cancer. A paracentesis should always be performed if pancreatitis is suspected, since detection of a very high amylase value in peritoneal fluid strongly favors this diagnosis.

The presence of a deeply lactescent serum is one of the most reliable means of diagnosing pancreatitis in a patient with acute abdominal pain.³ In fact, if one excludes the familial hyperlipemias it is the only abdominal crisis associated with this finding, aside from occasional diabetic ketoacidosis and isolated cases of systemic lupus erythematosus. The finding of hyperlipemic serum has particular diagnostic value, since it often coexists with normal serum amylase values.³

Since a number of conditions are associated with pancreatitis, an attempt should be made to determine a specific etiology;² chronic alcoholism or biliary tract disease account for the majority of cases. Recurrent renal calculi should suggest hyperparathyroidism. Attention should be paid to the use of certain drugs (especially steroids or thiazide diuretics) which have been implicated in acute pancreatitis. The patient should also be questioned about a family history of similar episodes, or recent trauma to the abdomen.

INFECTIOUS DISORDERS

In any patient presenting with acute abdominal pain accompanied by unusually high fever, chills, or profuse diarrhea, an infectious etiology or nonspecific inflammatory bowel disease should be a primary consideration. A history of recent travel, similar episodes in family members, or unusual food ingestion should be sought. When diarrhea is prominent, especially if the stools are mixed with blood, sigmoidoscopy should be performed and stools examined with the gram-stain technique for staphylococcus. If dysuria and flank tenderness are major complaints, acute pyelonephritis is a strong possibility.

In a female patient, acute pelvic inflammatory disease is probably the most common infectious disease simulating the acute abdomen; a careful history of sexual exposure, vaginal discharge, or onset of pain with menses should be sought. Gonococcal perihepatitis must be suspected under similar circumstances if symptoms are localized to the right upper quadrant. While rare in males, gonococcal periphepatitis should be suspected in a young man with urethral discharge and similar complaints.¹²

In a patient with localized, segmental complaints and no physical findings, a small area of vesicular eruption may point to early herpes zoster. Recently, acute nonspecific jejunitis was described.⁴ Obstructive symptoms and atypical abdominal pain characterize its clinical presentation. A barium study showing markedly thickened small bowel loops should restrain one from immediate surgery in patients with these findings.

REFERRED PAIN

Pain referred from other areas may present as an apparent abdominal crisis, but the absence of significant abdominal findings and careful search elsewhere for the primary site will usually establish the diagnosis. This is particularly true for diseases of thoracic origin, in which a chest x-ray and electrocardiogram should supplement clinical findings.

Renal Colic

The occasional intense vomiting, colicky pain, and deceptive radiation associated with renal colic could easily lead one to suspect an acute bowel obstruction. A history of passage of stones or gravel, the presence of dysuria or hematuria, and radiation of pain to the penis or testes are helpful clues to the diagnosis. Flank tenderness may be minimal or absent. This diagnosis should always be suspected in a patient with gouty arthritis and abdominal pain. Urinalysis and a scout film of the abdomen (for possible calcified stones) should be obtained before an intravenous pyelogram is performed.

Rectus Sheath Hematoma

Because this is uncommon it is rarely considered in the patient presenting with acute abdominal pain. The abrupt onset of severe pain localized to one quadrant, especially the right lower quadrant, after strenuous physical effort should immediately point to this condition.¹³ The diagnosis is established when a firm, nonmovable mass which does not cross the midline is present in the sitting and supine position. Attention has recently been drawn to the appearance of this complication in patients receiving anticoagulants.¹⁰

Neurologic

A radicular distribution of pain, with extension to the back after trauma or exertion, or in patients with known spinal disease, should suggest a nerve root compression syndrome. Careful neurologic examination is mandatory. The fulminant gastric crisis of tabes is a rare event

today, but the discovery of typical Argyll-Robertson pupils and posterior column deficits should prompt a VDRL test.

COLLAGEN-HYPERSENSITIVITY

Systemic Lupus Erythematosus

The presence of a history of other systemic features, especially joint, pleuropericardial, or skin manifestations, will usually make this diagnosis apparent. In patients with known systemic lupus erythematosus, the presence of acute abdominal findings confronts the clinician with a unique dilemma, since peritoneal signs may be prominent in active serositis.¹⁶ As a general rule, abdominal signs appearing concurrently with an exacerbation of the disease will indicate active serositis. The presence of profuse diarrhea or leukopenia supports the diagnosis. A paracentesis can be helpful since a sterile exudate is often found. A short course of high dose corticosteroids usually results in a dramatic reversal of symptoms but one must always be alert to the possible masking effects of steroids in a surgical condition.

Henoch-Schoenlein Purpura

This condition, described mostly in children, is probably often overlooked in adults.¹⁷ It is characterized by abdominal pain, joint symptoms, and purpuric eruptions, although not all features may be present in an individual patient. About two thirds of patients will develop joint symptoms either before or concurrently with the abdominal manifestations. Purpuric lesions involving the lower or upper extremities (but not the trunk) should call attention to this diagnosis. A barium study of the small bowel will demonstrate the distinctive features of submucosal edema. Renal involvement, seen in about one half the patients, may be manifested only by microscopic hematuria or proteinuria.

DRUG-TOXIN

Heavy Metals

Plumbism still constitutes a serious problem in children; a history of pica will bring the diagnosis to mind immediately. The problem may be much less obvious in an adult with abdominal pain, but the physician should be alerted by discovery of the rare blue-black lead line along the gingival margin, unremarkable abdominal examination, or motor weakness (especially wrist drop). A history of occupational exposure or use of lead impregnated food containers should be sought. While anemia with basophilic stippling is common and often unrelated to lead poisoning, elevation of serum lead is common and urinary delta amino levulinic acid (ALA) and coproporphyrinogens level is diagnostic.

Anticoagulants

The widespread use of these drugs has resulted in emergence of a number of gastrointestinal syndromes which may present with acute pain, including intramural bleeding in the bowel,³ rectus sheath hema-

toma,¹⁰ retroperitoneal hematoma, and (rarely) hemorrhagic pancreatitis. The prothrombin time is usually markedly elevated, but may be in the therapeutic range. The physician faced with this problem should proceed cautiously, observing the patient for development of a mass, and obtaining an upper gastrointestinal series which may reveal characteristic features of submucosal bleeding.

HEMATOLOGIC DISORDERS

Generally the underlying hematologic problem is apparent, as in sickle cell anemia, but rarely an unsuspected acute hemolytic crisis may result in severe back and abdominal pain. A history of dark or red urine, and presence of hemoglobinemia and severe anemia will establish the diagnosis.

On occasion, a bleeding disorder may be associated with abdominal pain secondary to hemorrhage into the bowel wall.¹² A barium study of the small bowel should confirm the diagnosis.

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Recognition and Management of Acute and Chronic Hepatic Encephalopathy

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Hepatic failure can manifest itself in a number of stereotyped ways. A patient may exhibit anasarca, variceal bleeding, hepatorenal failure, hepatic encephalopathy, or a combination of these. Each of these problems is challenging and represents a major threat to the patient's survival. Unfortunately, hepatic failure presents the physician with many unsolved therapeutic situations. Although our understanding of the pathophysiology underlying these conditions has broadened considerably, this has not yet led to major therapeutic breakthroughs.

Hepatic encephalopathy is defined as a neuropsychiatric syndrome consisting of intellectual deterioration, altered state of consciousness, and abnormal neurologic function in a patient with advanced liver disease or portal-systemic shunting.²¹

This is a rather open-ended definition and one should not accept as fact that a patient with liver disease who presents with an altered neuropsychiatric state has hepatic encephalopathy. Rather, it is a diagnosis of exclusion once other complications common to patients with advanced hepatic disease are ruled out. These include hypoglycemia, sepsis, electrolyte imbalance, central nervous system trauma, and drug intoxication.

The syndrome of hepatic encephalopathy has been investigated intensively during the last 10 years and a considerable amount of basic information has accrued. In addition, newer methods of treatment have evolved which are undergoing clinical trial. These advances will be the substance of this review.

CLINICAL FINDINGS

The clinical presentation of these patients has been well described^{20, 31} and will only be covered briefly here. The psychiatric syndromes⁴¹ that

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have been reported in these patients cover the entire spectrum of psychopathology. Initially, there may be inappropriate behavior and agitation, followed progressively by lethargy, stupor, and coma.

The neurologic manifestations are also variable.^{16, 20} Lethargic and stuporous patients may have no neurologic findings other than asterixis (liver flap) and hyperreflexia. Asterixis is a nonspecific finding and has been reported in other disorders such as diabetic ketoacidosis and uremia. Deeper coma may be accompanied by focal neurologic findings, pathologic reflexes, and decorticate and decerebrate rigidity. These findings can be transient and reversible. The pupils are small, symmetric, and reactive to light; these findings help differentiate this syndrome from a major acute structural central nervous system disorder. Hepatic coma is not readily differentiable from other metabolic encephalopathies such as barbiturate intoxication, hypoglycemia, and uremia. The characteristic odor of the breath, fetor hepaticus, may be helpful in the differential diagnosis. Another characteristic feature of hepatic encephalopathy is hyperventilation,²⁰ leading to respiratory alkalosis. Slowing of the electroencephalogram is a constant finding but is nonspecific, being found in almost all states with depressed cerebral functioning. Grand mal seizures are seen in some patients, but the incidence is low except in patients undergoing concomitant withdrawal of alcohol.

Chronic hepatic encephalopathy should be differentiated from the acute form. The chronic variety is seen most frequently in patients with established cirrhosis or in those who have had a portal-systemic anastomosis. Most of these patients are relatively stable, and the development of encephalopathy is usually due to iatrogenic factors such as administration of a sedative or diuretic, or to extrahepatic insult such as gastrointestinal hemorrhage, increased protein in the diet,²⁸ or sepsis. Thus, if these factors are eliminated or ameliorated one can usually anticipate improvement of the encephalopathy. In these patients the state of the liver disease, although advanced, may be stable or slowly progressive; thus, the physician has time to effect a therapeutic program.

In patients with acute hepatic injury and encephalopathy the opposite situation exists. These patients have massive hepatic necrosis, usually because of viral hepatitis or toxic factors, and treatment of their encephalopathy will usually be ineffective unless there is cessation of hepatic destruction and onset of regeneration. That is not to say that a similar clinical evaluation and treatment program should not be carried out, but the major emphasis has to be placed on restitution of hepatic function. Patients with the acute syndrome may have a fulminant course with the various stages of progressive encephalopathy telescoped into a day or two. Many of the early stages may be transient or inapparent, with stupor the main findings.

ETIOLOGY

The etiology of the central nervous system dysfunction in these states is still only partially understood. The theory of ammonia intoxica-

tion is supported by many observations in patients,^{7, 26, 43} as well as a vast experimental literature.³⁸ Measurements of arterial ammonia^{29, 43} correlate in a general way in patients with the chronic syndrome, but they are not as useful in the acute syndrome, and "estimation in terminal hepatic coma show wide fluctuance unrelated to the neurological condition."³³ Spinal fluid ammonia and glutamine levels⁴³ may correlate more closely with the neuropsychiatric state. Those situations which increase the load of ammonia presented to the central nervous system also adversely affect the syndrome and are often precipitating factors. These include gastrointestinal hemorrhage, systemic alkalosis,¹⁷ high protein diets, and the development of renal insufficiency. Conversely, therapeutic manipulations that reduce the ammonia load tend to improve the syndrome.

The molecular basis of "ammonia intoxication" is also not settled. The brain can only metabolize ammonia via combination with alpha-ketoglutarate to form glutamic acid. Another molecule of ammonia can combine with glutamic acid, forming glutamine. Alpha-ketoglutarate is a major intermediate in the citric acid cycle and thus, a major factor in ATP synthesis. The major source of systemic ammonia is derived from the hydrolysis of gastrointestinal urea.³³ The concentration of ammonia in portal vein blood is approximately five times that of systemic venous blood. In the liver, ammonia is extracted and is metabolized via the Krebs-Henseleit cycle to urea. Because of its high diffusibility, large quantities of urea enter the gut lumen⁶ and are hydrolysed mainly by bacterial ureases in the colon to ammonia. Thus, there is an enterohepatic circulation of ammonia and urea with approximately 3.5 gm. of ammonia formed per day.

In acute animal experiments using large loads of ammonia administered intravenously, a variety of metabolic abnormalities have been encountered.

Shenker et al.¹⁵ have reported that ATP and phosphocreatine levels are depressed in the brain stems of such animal preparations, but not in the cerebral cortex. Alpha-ketoglutarate levels were normal in both brain stem and cerebral cortex of the ammonia-intoxicated rat. The mechanism leading to reduction of energy-rich phosphate bonds in the brain stem is still poorly understood. It is tempting to speculate that this could lead to a depression of the reticular activating system and hence to coma. Another interesting study performed by Warren and Shenker⁴⁰ involved the inhibition of glutamine synthesis by blocking the enzyme glutamine synthetase with methionine sulfoxime. In these blocked animals the toxicity of ammonia was markedly reduced.

There are clinical situations in which the role of ammonia is less clear. Thus, in fulminant hepatic failure arterial ammonia levels may not correlate with the patient's clinical state² and therapeutic methods which decrease ammonia are ineffective. There is a lag of 12 to 24 hours⁷ between the rise of serum ammonia level and neuropsychiatric deterioration, and this may in part explain the poor correlation.

Short-chain fatty acids have been implicated in the pathogenesis of hepatic encephalopathy.^{18, 26, 43} Short-chain fatty acids (4 to 8 carbons) have been reported to be elevated in the plasma of some patients with

hepatic failure. The administration of short-chain fatty acids can induce reversible coma in experimental animals.²¹ Additional evidence comes from the study of patients with the inherited metabolic disease, isovaleric acidemia.³⁴ When the level of isovaleric acid is further elevated by high protein intake or infection, stupor can supervene.

The mechanism of action of short-chain fatty acids in inducing stupor and coma is as yet obscure. In recent *in vivo* animal studies, Walker et al.²¹ did not find abnormalities in the ATP content of brain stem or cerebrocortical tissues following short-chain fatty acid-induced coma. The effect may be at the level of the neuronal cell membrane.²⁶

In patients with acute hepatic failure, one of the causes of encephalopathy may be cerebral edema. Ware et al.³⁹ found post mortem evidence of cerebral edema in 16 of 32 patients who died with massive hepatic necrosis. Four of the 16 patients had evidence of cerebral herniation. There is as yet no evidence that specific treatment aimed at reducing brain swelling has improved the encephalopathy, but this may be a rational approach in the patient with acute hepatic failure in whom deep coma does not respond to the usual therapy. Lumbar puncture should be avoided, and the diagnosis has to be made on rather tenuous grounds unless papilledema is present.

The neurochemical theory of hepatic coma has recently been revived with the use of levodopa in the treatment of hepatic encephalopathy.^{10, 11, 19} Proponents of this theory postulate that there is either a depletion of neurochemical transmitters (e.g., norepinephrine and dopamine) in certain vital areas of the central nervous system or there are "false neurochemical transmitters which displace biologically active neurotransmitters from neuronal receptor sites."¹⁰ Amino acids can be degraded by the gut flora to form false neurochemical transmitters. Phenylalanine and tyrosine, when acted upon by bacterial decarboxylase, form phenylethylamines which are potent false neurochemical transmitters. Under normal circumstances these are largely cleared from the portal blood by the liver. This theory is further supported by the effectiveness of oral antibiotics in treating hepatic encephalopathy. Fischer¹⁰ measured the urinary excretion of octopamine, a false neurochemical transmitter, in patients and in the central nervous system of animals with advanced hepatic failure. He found elevated levels in both groups and a correlation with degree of liver injury.

TREATMENT

At this time the basic approach to the patient with either acute or chronic hepatic encephalopathy is still aimed at reducing the ammonia load presented to the nervous system, although, in fact, the effectiveness may be due to a reduction in deleterious products of protein metabolism other than ammonia. Protein has to be completely eliminated from the diet until the patient is alert. Cathartics and enemas are administered to eliminate nitrogenous material from the colon. Magnesium sulfate is an excellent cathartic in these patients and may have the additional advantage of repleting low body magnesium stores.

The oral or rectal administration of poorly absorbed antibiotics has proven to be of great value in hepatic encephalopathy. The presumed mechanism of action is through reduction of intestinal bacterial urease activity. In chronic use it may be effective despite re-emergence of urease-producing bacterial flora. Neomycin is currently the drug of choice and it can be administered orally or via retention enema. The oral dose is 3 to 8 gm. per day. Enemas are prepared using 1 to 2 gm. of neomycin in 100–200 ml. saline. Because of possible systemic accumulation⁸ of the drug in patients with renal insufficiency, the substitution of a nonabsorbable sulfonamide such as succinylsulfathiazole or phthalylsulfathiazole may be preferable to avoid the risk of nephrotoxicity. Neomycin if used on a chronic basis can be toxic to the small intestinal mucosa leading to malabsorption.

Scrupulous attention has to be paid to establishing and maintaining electrolyte and acid-base balance. Hypokalemia is especially dangerous as the associated alkalosis increases the load of ammonia presented to the central nervous system because of non-ionic diffusion.* The associated intracellular acidosis “traps” the ammonia by titration back to the ammonium ion. In addition, it has been shown that hypokalemia increases the concentration of ammonia in renal venous blood.³⁰

Hypoglycemia is frequently encountered in patients with fulminant hepatic necrosis.⁹ These patients have reduced liver glycogen stores and have decreased capacity for hepatic gluconeogenesis. We favor continuous infusion of 5 per cent dextrose solution in these patients. If renal failure develops, more concentrated solutions of dextrose can be infused into a large vein via pump.

Lactulose^{4, 32, 42} is a disaccharide (1-4 betagalactosido-fructose) which has been used successfully in treating portal-systemic encephalopathy. This disaccharide is not absorbed by human intestinal mucosa and is degraded in the large bowel by the bacterial flora. The main products of this bacterial fermentation are acetic and lactic acids which lower fecal pH. The low pH is thought to suppress bacteroides, a potent urease-producing organism, and to foster the growth of lactobacilli. Lactulose can be therapeutic via several mechanisms: (1) reduction of fecal pH leading to reduced ammonia absorption via non-ionic diffusion,* (2) suppression of bacteroides species, a major source of intestinal urease activity, (3) induction of an osmotic type of diarrhea which diminishes fecal stasis and reduces nitrogenous substrates for ammonia production.

Bircher[†] found that lactulose could be substituted for neomycin without ill effects in chronic patients. The dose ranged between 15 to 140 gm. a day in divided doses. In some patients neomycin is more beneficial than lactulose while in others lactulose has been effective where neomycin failed. Most impressive has been the successful use of lactulose in hepatic coma precipitated by gastrointestinal hemorrhage. Other than diarrhea, which is dose related, lactulose has no significant known side effects. Its use would thus seem to be preferable to neomycin on a chronic

* As the pH is raised the ammonium ion is titrated to ammonia ($\text{NH}_4^+ + \text{OH}^- \rightleftharpoons \text{NH}_3 + \text{H}_2\text{O}$).
Biologic membranes are more permeable to this un-ionized moiety.

basis, but, unfortunately, lactulose has not as yet been approved for use in the United States.

The use of levodopa in the management of patients with hepatic coma has been reported by Parks¹⁹ and Fischer.^{10, 11} These authors report prompt electroencephalographic improvement followed by arousal in 8 patients in deep coma. An oral dose of 3.5 to 5 gm. per day in divided doses has been used. The action of levodopa is presumably to replete dopamine stores in the central nervous system. Among the many side effects of levodopa which may limit its usefulness is a tendency to cause gastritis and gastrointestinal bleeding. Parenteral administration of this drug may overcome this problem.

In an attempt to remove the elusive "toxins" that are responsible for hepatic encephalopathy a number of "blood-cleansing" procedures have been advocated.

Exchange transfusion is probably the method with which there has been the most experience. There have been some dramatic clinical responses with this technique both in acute and chronic encephalopathy.^{2, 11, 36} The Fulminant Hepatic Failure Surveillance Study³⁵ has collected data on over 600 patients. The age-corrected survival without treatment is approximately 10 per cent. Those patients who have been treated with exchange transfusion has a survival of approximately 20 per cent. This seems to be a significant improvement. However, this is not a controlled study and may merely represent a trend. In extensive surveys,^{5, 15, 22, 23} minimal improvement and few long term survivors have been noted in groups of patients treated by exchange transfusion. Most significantly there was high incidence of sepsis, unexplained fevers,²² and gastrointestinal bleeding. This procedure also has the potential of spreading the infection to hospital personnel when viral hepatitis patients are exchanged.

Recently, a rather aggressive approach has been adopted by Klebanoff et al.¹¹ In this study the patient's blood was replaced with chilled Ringer's solution until the hematocrit was close to 0 per cent. The patient was then rewarmed with the infusion of fresh blood. Because of the potential side effects, the procedure cannot be recommended at this time.

Peritoneal dialysis and hemodialysis^{13, 22} have been used sporadically for management of hepatic failure. Theoretically this approach has merit, especially in those patients with combined encephalopathy and hepatorenal failure. It certainly is effective in treating the uremic state, and the removal of urea should lower the ammonia load presented to the central nervous system.

We have had personal experience with 5 patients with alcoholic cirrhosis who were admitted with encephalopathy and hepatorenal failure. Presumably these patients had the acute insult of alcoholic hepatitis superimposed on chronic cirrhosis. The patients underwent peritoneal dialysis both for encephalopathy and hepatorenal failure. They were also treated with large doses of corticosteroids. Three patients responded with improvement of their encephalopathy and reversal of renal failure, temporally related to the dialysis. Only 1 patient survived; the other 2 succumbed to sepsis and gastrointestinal hemorrhage. A similar experience

has been reported by Ritt.²² Dialysis can reverse the hepatic encephalopathy in some cases, but here once again the relentless progression of hepatic necrosis or associated complications such as gastrointestinal hemorrhage mitigate against long term survival.

Another approach to the patient with acute hepatic failure and severe unresponsive encephalopathy is represented by the cross circulation and liver perfusion studies recently reported.^{1, 5, 25} In these reports patients have been treated by perfusion of their blood through various animal and human liver preparations. There have been some notable successes, but as yet the techniques and complications limit its use to a few centers. It is also difficult to establish whether these procedures, with their risks to the patient, great expense, and consumption of physician time, offer any significant advantages over the other methods enumerated above.

SUMMARY

We have reviewed the recent developments with regard to the pathogenesis of hepatic encephalopathy and conclude that ammonia intoxication is still the most likely pathogenetic mechanism although the molecular basis of its action is still in question.

We also have reviewed the therapeutic approach in these patients and conclude that the syndrome, when it occurs in patients with chronic liver disease or in patients with portal-systemic anastomosis, responds relatively well to conservative management designed to lower systemic ammonia levels. The use of levodopa may eventually prove to be an important addition to our therapeutic regimen.

Patients who have acute massive hepatic necrosis may respond to some of the measures with transient improvement of the encephalopathy but their survival rate is dismal. In these patients the immediate problem is widespread, and continued loss of liver cells and the encephalopathy is a preterminal event.

Until specific measures are available which can restore liver function, measures such as exchange transfusion, dialysis and liver perfusion cannot be considered definitive therapeutic approaches. They may be used to stabilize the patient and thus gain time to perform a more definitive procedure such as hepatic transplantation. It was hoped that the time gained by these procedures would allow hepatic regeneration to occur, but in fulminant hepatic necrosis this has rarely been the case.

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Acute Renal Failure

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Acute renal failure refers to sudden and usually transient reduction in glomerular filtration rate, with or without oliguria. Such a situation may be prompted by obstruction, reduced renal perfusion, various glomerulitides, vasculitides, or toxins (i.e., antibiotics, chemicals, hemoglobin, myoglobin), and a variety of miscellaneous factors. This discussion is primarily concerned with acute parenchymal renal failure due to what has been termed "acute tubular necrosis".

It has been recognized that although the term acute tubular necrosis implies that renal tubular cells are necrotic and thus dysfunctional, such a simplified viewpoint is not always evident in histologic or functional studies.^{7, 22} Patients who develop acute parenchymal renal failure with similar clinical settings, findings, and courses may show microscopic evidence of acute tubular necrosis, acute interstitial nephritis, or no obvious pathology.

The classification of apparent acute renal failure into prerenal, renal, and postrenal considerations is still useful. Such designations direct the physician's attention to broad diagnostic and therapeutic implications.

Postrenal failure refers to obstruction. The possibility of obstruction is usually suggested by the total absence of urine output (anuria) in the presence of normal or enlarged kidneys as viewed on a flat plate of the abdomen. Anuria may also be caused by acute glomerulonephritis, cortical necrosis, or bilateral renal arterial thromboembolism. It is sometimes present during the first 12 to 24 hours of acute tubular necrosis. Anuria alternating with periods of polyuria is also strongly suggestive of obstruction. Oliguria (volumes of less than 400 ml. per day) may also be associated with obstruction. Possible obstruction is investigated by retrograde pyelography. Examination of one ureter is usually sufficient. Intravenous pyelography has been helpful in some oliguric patients.³

PATHOPHYSIOLOGIC DIFFERENTIATION OF PRERENAL AND PARENCHYMAL (RENAL) FAILURE

The dynamics associated with prerenal and true parenchymal renal failure may be approached by considering the sequence occurring with

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blood loss. As blood volume decreases, vascular capacity and organ perfusion are diminished, with relative maintenance of cerebral and coronary blood flows. The kidneys share in these events with increased renal vascular resistance and decreased renal blood flow. As renal blood flow decreases, glomerular filtration rate is reduced, but to a lesser degree. Filtration fraction, the portion of renal blood flow that is actually filtered through the glomeruli, is thus increased. Such a situation implies relatively greater efferent arteriolar constriction with increased glomerular capillary pressures and lower post-efferent arteriolar and peritubular capillary pressures. In addition, the increased filtration fraction results in an increased concentration of nonfiltered protein in the peritubular capillary networks. These factors tend to promote proximal tubular sodium reabsorption accompanied by diffusion of chloride, water, and urea.²⁶ Reduced blood volume causes increased secretion of antidiuretic hormone, with resultant increased water and urea absorption in the collecting ducts.

In comparison to the movement of urea within the nephron, there is relatively little reabsorption or secretion of creatinine. Thus, although the filtration of urea and creatinine is impaired to the same degree because of the reduced glomerular filtration rate, there is comparatively greater retention of urea than creatinine owing to the passive reabsorption of urea. These factors contribute to the increased blood urea nitrogen:serum creatinine ratios noted with prerenal azotemia.

Reduction in blood volume also causes the release of renin from the afferent arteriolar juxtaglomerular apparatus. Renin acts on a plasma substrate, causing the formation of angiotensin I, a decapeptide which is further converted to the octapeptide angiotensin II, primarily in the lungs but also in the kidney. In addition to its effects as a potent vasoconstrictive agent, angiotensin II stimulates secretion of aldosterone by the adrenal cortex. Aldosterone acts primarily on the distal tubule to cause further reabsorption of sodium.

Furthermore, the kidney that is poorly supplied with blood may undergo redistribution of blood flow, with shunting of blood through juxtamedullary nephrons at the expense of renal cortical blood flow.¹³ Cortical ischemia may be demonstrated by xenon techniques and is also clinically evident in angiographic studies. The juxtamedullary nephrons are longer and presumably more capable of promoting sodium reabsorption, the assumption being that the relatively greater juxtamedullary blood flow stimulates greater sodium reabsorption.

The foregoing factors and events occurring in the patient with prerenal failure tend to produce a concentrated urine that is reduced in volume and has a low sodium concentration. In contrast, the kidney that has been damaged by acute tubular necrosis does not respond in this way. The scanty urine which is excreted contains a high concentration of sodium and has an osmolality close to that of glomerular filtrate.

Three basic mechanisms have been offered to explain the pathophysiologic findings in acute tubular necrosis: (1) intratubular obstruction with necrotic debris; (2) back-diffusion of glomerular filtrate across damaged tubular cells;¹ (3) pronounced afferent arteriolar constriction as opposed to the efferent constriction predominating in the prerenal situa-

tion.²⁵ (Evidence for the presence of relatively greater afferent arteriolar constriction has been shown for both ischemic and nephrotoxic acute renal failure.¹²) The last mechanism appears to be the dominant one.

Renin and angiotensin levels are elevated in patients with acute tubular necrosis.^{1, 29} Renin levels tend to remain high during the period of oliguria, and fall with the onset of diuresis. Laboratory animals are protected from glycerol-induced acute renal failure by previous salt-loading, presumably as a result of lowered renin levels. The role of the renin-angiotensin system is further evidenced by the suggestion that glycerol-challenged rats are protected from the clinical expression of acute renal failure by prior treatment with anti-renin antibodies.²⁴

AIDS IN THE DIAGNOSIS OF ACUTE RENAL FAILURE

STATE OF HYDRATION, BLOOD PRESSURE, AND CARDIAC OUTPUT. It is physiologically proper for patients who are dehydrated or hypotensive to have reduced renal blood flow and consequently reduced urine output. Before consideration is given to the definitive diagnosis of acute tubular necrosis in such patients, their blood volume and fluid deficits should be rapidly repleted.

URINE VOLUME. Oliguria occurring in a nonhypotensive individual who is adequately hydrated and does not have severe heart failure should signal the possibility of acute renal failure. Some patients may show markedly reduced glomerular filtration rates with progressive elevation of blood urea nitrogen and serum creatinine, and develop acute renal failure in association with normal or high urine output. Such "high-output" renal failure has been reported in a number of clinical situations. The onset of acute renal failure may be overlooked if urine volume is the only index monitored. A clinical setting conducive to acute renal failure should prompt repeated surveys of blood urea nitrogen, creatinine, and serum potassium, as well as urine volume.

URINE CONCENTRATION. The urine excreted by patients with acute tubular necrosis is neither concentrated nor dilute. Urine specific gravity is misleadingly increased by the presence of cellular elements and fragments, while osmolality is negligibly altered by such debris. In the presence of oliguria, the ratio of urine osmolality to plasma osmolality is a more reliable index and requires just 3 ml. of each fluid. A ratio of less than 1.2 to 1 is suggestive of acute tubular necrosis or acute interstitial nephritis. Ratios of 2 or 3 to 1 are usually seen with prerenal oliguria.¹¹

Similar information may be implied from the concentration of urea excreted. The urine urea nitrogen to blood urea nitrogen ratio (UUN:BUN) is less than 10:1 in acute tubular necrosis. The ratios are considerably higher with prerenal states. Similar findings are seen with urine creatinine to serum creatinine ratios, but the UUN:BUN studies are usually much more readily available as emergency determinations.

URINE SODIUM CONCENTRATION. Urine sodium concentration is usually less than 30 mEq. per liter in prerenal states and 50 to 90 mEq. per liter in acute tubular necrosis. When oliguria persists for several days

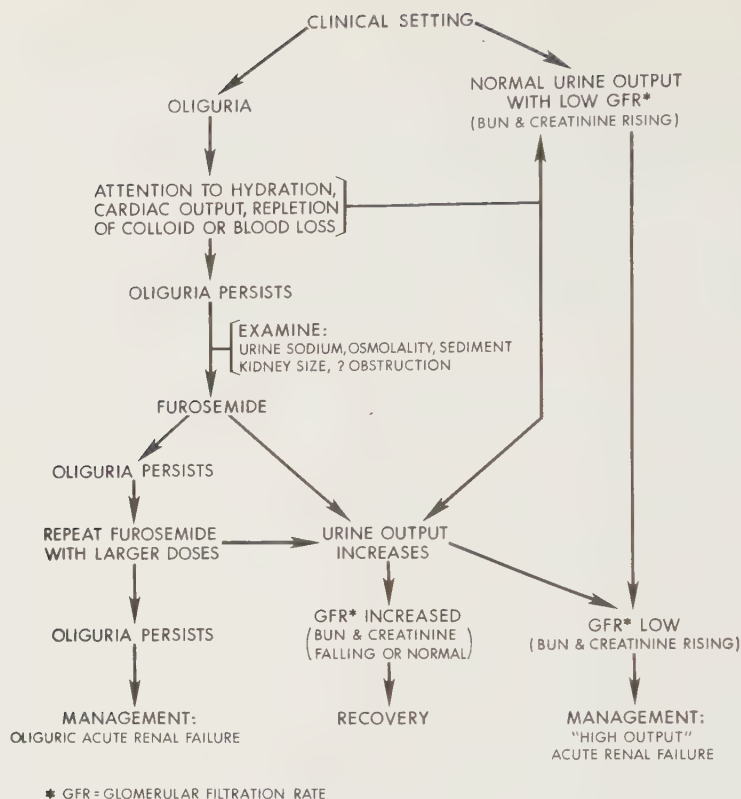


Figure 1. A sequential approach to the diagnosis of acute renal failure.

in patients with acute tubular necrosis, the urine sodium concentration may fall to levels consistent with those seen in prerenal states.

URINARY SEDIMENTS. The urine sediment is normal in patients with prerenal azotemia unless there is a pre-existing cause for abnormal sediment. With acute tubular necrosis the urine contains tubular cells, casts, and protein.

RESPONSE TO FUROSEMIDE. The response to furosemide is of diagnostic and therapeutic importance. Furosemide is administered to the oliguric patient in an initial dose of 40 mg. intravenously. The dose is doubled until a response is noted. Doses as high as 3000 mg. have been given with beneficial results.

Transient nerve deafness has been described with the use of large doses of furosemide in patients with renal failure,²⁷ but the reported incidence appears to be less than with ethacrynic acid.²³ Although the permanent nerve deafness ascribed to ethacrynic acid has not yet been reported with the use of furosemide, patients receiving large doses of furosemide should be repeatedly examined for hearing loss, particularly when other ototoxic agents are simultaneously administered.

Furosemide may produce three results when administered to oliguric patients in a setting conducive to acute renal failure (See Figure 1): (1) The urine output may increase with appropriate increases in glomerular filtration rate. Such patients may go on to uneventful recovery with apparently normal renal function. (2) The urine volume may increase but the increased output is associated with a persistently low glomerular filtration rate, rising blood urea nitrogen and creatinine levels, and all the features of "high output" acute renal failure. In such cases, repeated administration of furosemide may be necessary for the maintenance of normal urinary output, a factor which may ease sodium and fluid restrictions during the treatment of acute renal failure. (3) There may be no response even to large doses of furosemide. Such patients are managed as oliguric acute renal failure patients.

In some cases there may be considerable difficulty in deciding whether acute or chronic renal failure is present. Normal or slightly enlarged kidneys demonstrated radiographically suggest acute renal failure, while small kidneys would be consistent with chronic renal failure. Renal biopsy may be indicated in patients with normal kidney dimensions in whom the differential diagnosis or the patient's course includes considerations that would alter the therapeutic approach to the patient's intrinsic kidney disease.

COURSE

The oliguric stage of acute tubular necrosis usually lasts for 8 to 16 days. Almost all patients will have begun to show a diuresis by the twenty-first day. Rare cases have been described with longer oliguric periods: patients with acute renal failure following methoxyflurane anesthesia may have persistent, apparently irreversible oliguria for more than a year.¹⁴ For practical purposes, however, failure to enter the diuretic phase by the end of the third week should raise the possibility of an alternative diagnosis.

Cortical necrosis is a prime consideration in such cases. Cortical necrosis may occur as a result of the initial insult, particularly in association with obstetrical problems, or possibly as a consequence of complications occurring during the course of acute tubular necrosis.⁵

Two kinds of clinical expression of acute renal failure may be identified. The patient who suffers acute renal failure in association with severe trauma, surgery, or infection is more likely to show a *hypercatabolic* course; the patient with acute renal failure without such serious accompaniments would be expected to show a milder course. The presence of perforated viscera, peritonitis, massive soft tissue damage, serious infection, heat stroke, or large quantities of blood in a "third space" (retroperitoneal hemorrhage, hematoma in fascial planes), are factors which seriously complicate the course and management. Wound healing may be significantly impaired in patients with renal failure.

The rate of rise of the blood urea nitrogen during the first few days of acute renal failure is approximately 25 to 35 mg. per 100 ml. per day in

patients with uncomplicated acute renal failure, while patients with hypercatabolic acute renal failure may show blood urea nitrogen increments of as much as 60 to 90 mg. per 100 ml. per day. Serum creatinine usually rises 2 to 3 mg. per 100 ml. per day, but may rise much more rapidly, out of proportion to the rate of rise of blood urea nitrogen, in cases complicated by severe muscle necrosis.⁹

In addition to the severity of expression of the uremic syndrome, the hypercatabolic patient is at greater risk of developing life-threatening hyperkalemia. In some cases, deadly hyperkalemia may arise within hours.

MANAGEMENT

Hyperkalemia

Hyperkalemia⁷ is a common accompaniment of acute renal failure. Serum potassium determinations and electrocardiograms are helpful in monitoring patients. Whenever possible, serum potassium levels should be correlated with electrocardiographic changes in a given patient so that the electrocardiogram may be used when serum potassium determinations are not immediately accessible. Serum potassium levels above 6.0 mEq. per liter, or electrocardiographic changes showing widening of the QRS intervals and reduction in atrial activity, should be treated as emergencies in patients with acute renal failure. Patients with markedly elevated potassium levels (8.0 mEq. per liter), particularly those with associated hyponatremia, may show excitability, mania, dilated pupils, hyperpnea, tachypnea, marked weakness, and bradycardia. (Occasional patients may present with ventricular tachycardia.) Such findings should prompt an immediate electrocardiogram and serum potassium determination.

The emergency treatment of life-threatening hyperkalemia reflects the antagonism of sodium and calcium ions to the effects of the potassium ion, and the effects of pH adjustments on the concentrations of potassium across cell membranes. Hypertonic sodium bicarbonate should be rapidly infused intravenously, and electrocardiographic monitoring begun or continued. Sodium bicarbonate will provide high concentrations of sodium and rapidly raise blood pH. In most cases, dramatic electrocardiographic improvement will be noted within minutes. Calcium gluconate or calcium chloride, given intravenously, will also be helpful and will serve to counteract the tendency to produce tetany caused by the rapid elevation of the blood pH in a uremic patient. The calcium preparations should be given separately from bicarbonate solutions to prevent precipitation of calcium salts. Fifty per cent glucose and insulin (1 unit of insulin for each 5 gm. of glucose) will also be helpful.

These measures will control hyperkalemia in most patients for half an hour to 3 hours. More definitive control should be sought simultaneously. An ion exchange resin (sodium polystyrene, Kayexelate) should be administered by mouth in a dose of 10 to 20 gm., with 30 to 60 ml. of Sorbitol, an osmotic cathartic. Kayexelate may also be given rectally in doses of 50 gm. per enema. Prolonged, definitive control of serum potas-

sium levels may be achieved in most cases by the prompt institution of potassium-free peritoneal dialysis while the above measures are being instituted. Peritoneal dialysis serves as an effective intermediate term preventative against pronounced hyperkalemia. However, in occasional patients with hypercatabolic acute renal failure, control of hyperkalemia may not be achieved with peritoneal dialysis and the above measures. Such patients require hemodialysis.

Fluids

Patients with acute renal failure lose water primarily by insensible loss (sweating, expired water vapor), by excretion of urine, and incident to complications (diarrhea, tube drainage, vomiting). Water is gained by the combustion of carbohydrates, fats, and protein.^{18, 19} This water of catabolism amounts to approximately 300 to 450 ml. per day for the average patient. Since insensible losses amount to approximately 800 to 1000 ml. per day in patients of average size, a simplified approach to daily fluid replacement would be to administer 400 to 500 ml. of fluid plus an amount equal to the 24 hour volume of urine excreted, plus an amount equal to the volume lost by other routes (diarrhea, vomiting, tube drainage, sweating, etc.). Calculations may be made on a 24 hour basis or at shorter intervals in rapidly changing situations. These rough guidelines are clinically adequate since the accuracy of replacement is monitored by accurately weighing the patient at least daily. Most adult patients who receive appropriate fluid replacements lose three fourths to 1 lb. per day, although patients with hypercatabolic acute renal failure may lose as much as 2 lb. per day.

Sodium

Uncomplicated oliguric patients have negligible sodium losses; sodium is withheld from such patients. Those with diarrhea, tube drainage, "high-output" renal failure, or other features which cause sodium loss, may lose significant quantities of sodium, which should be replaced in accordance with estimates based on actual spot determinations of fluids lost.

Infection

Infection causes serious morbidity and considerable mortality in patients with acute renal failure. Indwelling urethral catheters should not be used unless absolutely necessary. Frequent examinations and revisions of intravenous access sites are important.

Although prophylactic antibiotics are not used, high degrees of suspicion and vigilance are warranted together with prompt and vigorous treatment of identified infections. The use of antibiotics should be tempered by the necessity for adjustments of doses in patients with renal failure.²

Circulatory Overload

Dyspnea, orthopnea, tachycardia, pulmonary congestion, elevated venous pressure, and edema may result from circulatory overload, owing to

excessive extracellular fluid volume. Dialysis may be required in such situations. Digitalis should be used only when true myocardial failure is suspected.

Calories

The provision of at least 600 calories per day will significantly decrease the catabolism of endogenous protein and the consequent production of sulfates, phosphates, and potassium. A high caloric food free of sodium, potassium, and protein may be provided by mixing equal parts of Karo syrup (4 calories per ml.) and iced ginger ale. Similar commercially prepared solutions are available. The preparations are administered to oliguric patients in keeping with calculated fluid restrictions. Oliguric patients who cannot take oral fluids may be temporarily provided with calories by the infusion of appropriate amounts of 50 per cent glucose (200 calories per 100 ml).

Acidosis

Acidosis is almost invariably present. In most cases, the degree of acidosis becomes stable at a blood pH of 7.2 to 7.3 with a serum bicarbonate of 12 to 20 mEq. per liter. Stabilization probably reflects a significant buffering effect of bone in addition to respiratory compensation. Treatment is not required in such cases. More severe acidosis, with its attendant risk of serious hyperkalemia, should be treated with sodium bicarbonate.

Anemia

The anemia of uremia becomes evident within the first week of acute renal failure. Experience with patients with chronic renal failure who receive maintenance hemodialysis supports the view that stable hematocrits of 15 to 20 per cent should not prompt transfusion, unless there is evidence of air hunger or deleterious cardiac effects. Patients with bleeding or hemolysis may require transfusions to maintain hematocrit levels above 15 per cent.

Coagulopathy

The coagulopathy of uremia, featured by decreased platelet adhesiveness and deficient production of platelet factor 3, may cause bleeding after several days of acute renal failure. Gastrointestinal bleeding, commonly associated with uremic gastroenteritis, is usually evidenced by occult blood in the stool or in gastric aspirates. Brisk or massive gastrointestinal bleeding is usually due to frank peptic ulceration or diverticulitis. The coagulopathy of uremia may foster continued bleeding in such patients.

Dialysis

Even with the most successful attention to clinical details, patients who are managed without dialysis are likely to be quite ill after several days of acute renal failure. The use of prophylactic supportive dialysis^{6, 28} allows for the liberalization of fluid, protein, and sodium intake, facili-

tates wound healing, reduces the predisposition to infection, and diminishes the bleeding tendency. It is our practice to provide peritoneal dialysis for most patients when the serum creatinine reaches 12 to 15 mg. per 100 ml. or when blood urea nitrogen reaches 100 mg. per 100 ml. Hypercatabolic patients and those with extensive tissue injury or who are postoperative, as well as those with bleeding, pericarditis, infection, or serious hyperkalemia, receive immediate dialysis. In such cases, peritoneal dialysis is repeated at least twice weekly. Hemodialysis is used for patients who are markedly hypercatabolic with poor response to peritoneal dialysis, or for those in whom peritoneal dialysis is technically not feasible.

DIURESIS

The onset of diuresis, indicative of progressive recruitment of functioning nephrons,²¹ is heralded by a progressive increase in urine output and the achievement of a urine volume of at least 2 liters per day. The blood urea nitrogen and serum creatinine usually continue to rise 1 to 3 days following the onset of diuresis, indicating that the rate of increase in urine volume is greater than the increase in glomerular filtration rate. Although most patients improve dramatically with the onset of diuresis, occasional patients will require additional supportive dialysis during the early diuretic phase.

Fluid and sodium intake should be increased in keeping with the increased urine output. Protein and potassium intake may be liberalized as the blood urea nitrogen and creatinine fall. In general, uncomplicated patients may ingest regular diets and sufficient fluids to quench thirst during the diuretic phase without incurring major balance difficulties. Weight, blood urea nitrogen, and serum potassium levels should be monitored daily to assure proper resolution and balance.

Massive diuresis (greater than 4 liters per day) is unusual for patients who have been properly managed during the period of oliguria. If fluid balance has been correctly managed the urine output will usually level off at between 2 to 3.5 liters per day. The excreted urine contains 30 to 60 mEq. of sodium per liter.

Occasional patients, particularly those with extensive soft tissue injury, may show hypercalcemia during the diuretic phase, presumably because of continuing, although decreasing, secondary hyperparathyroidism, or perhaps because of the reabsorption of soft tissue calcifications.^{8, 17} The situation is self-limited and does not require specific therapy other than the maintenance of proper hydration and the provision of adequate sodium intake.

Sixty to 70 per cent of patients recovering from acute tubular necrosis achieve normal glomerular filtration rates.^{10, 16} Older patients, or those with longer periods of oliguria or ischemic lesions, are less likely to achieve a return to normal glomerular filtration rates. Patients who do not show a return to normal have glomerular filtration rates above 60

per cent of normal. Since a 50 to 60 per cent reduction of glomerular filtration rate is usually necessary before blood urea nitrogen and creatinine concentrations rise to abnormal levels, it is expected that almost all patients recovering from acute tubular necrosis will show normal blood urea nitrogen and creatinine levels by the second month following recovery, and that a minority of patients will have moderate renal insufficiency with high blood urea nitrogen and creatinine during periods of renal stress.

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Sickle Cell Crisis

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Crises in patients with homozygous sickle cell disease (SS), and in patients doubly heterozygous for sickle and an allelic abnormal hemoglobin gene (e.g., SC, SD, or S-thalassemia), have classically been divided into 3 types: painful, aplastic, and hemolytic. In addition to these crises, patients with such sickling disorders are also subject to increased morbidity during pregnancy, surgery, or as a consequence of infection, dehydration, trauma, or other stressful disturbance. The management of the sickle cell patient with "crisis" must, therefore, include a consideration of these problems as well.

The proper care of the sickle cell patient under stress, that is, either in crisis or in a situation which may precipitate some serious complication of this disease, requires an understanding of the pathophysiology of the sickling phenomenon. Sickling of erythrocytes is the consequence of an abnormal polypeptide structure of hemoglobin in which valine is substituted for glutamic acid in the sixth position from the N-terminal end of the beta chain. This single amino acid substitution profoundly alters the properties of the hemoglobin molecule such that in a deoxygenated state the hemoglobin is less soluble and precipitates as a result of intermolecular rearrangements. These form crystalline aggregates which distort the cell into its characteristic sickle shape.¹³

Potentiating the sickling of deoxygenated hemoglobin are conditions not infrequently encountered clinically. For example, acidosis and increased osmolality are known to increase the sickling of SS blood.^{1, 22} Consequently, conditions which lead to a disturbance in the homeostasis of body water and electrolytes, such as may occur with vomiting, fever, or disturbed renal function, may induce a crisis by potentiating sickling. The inability of adult patients with SS disease to conserve water because of a defect in renal concentrating ability^{16, 24} predisposes them to dehydration.

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The distorted shape of the sickle cell, changes in red cell membrane, and the presence of irreversibly sickled cells (cells which will not unsickle even when oxygenated) lead to increased whole blood viscosity and predispose to sludging in the microcirculation.⁹ It is evident, therefore, that any disturbance which enhances this phenomenon can further impair flow integrity and induce the ischemic obstruction and infarction which characterizes the typical painful crisis of sickle cell disease. All such crises must be considered serious and life-threatening, for if they involve a vital organ, death can be the final consequence.

In addition to the impaired rheology of sickle cell disease, the abnormal cell is subjected to constant destruction by the reticuloendothelial system. This leads to anemia, persistent jaundice, and increased excretion of bilirubin as a result of the excess heme catabolism. The hematologic findings in a patient with SS disease even when not in crisis are characterized by anemia, reticulocytosis, leukocytosis, and not infrequently, thrombocytosis.

The doubly heterozygous disorders associated with the sickle gene such as SC, SD, and S-thalassemia are subject to similar problems but, as a rule, are not as severe as the patient with homozygous SS disease. Nevertheless, the management of a crisis in these patients is similar to that of a crisis in an SS patient.

PAINFUL CRISIS

This is the most common type of crisis and the most disturbing to the patient. It is seen more often in homozygous sickle cell disease than in one of the variants mentioned above. The frequency of painful crisis may vary from patient to patient despite what appears to be an identical hemoglobinopathy. The crisis may be precipitated by a respiratory infection or may arise *de novo*. Pain is often severe, and frequently tends to follow a recognizable pattern in a given patient. Because leukocytosis is frequently seen in sicklemic patients with or without crises, the simultaneous occurrence of pain and fever may make it difficult to exclude the presence of an infectious process. For example, one of our patients with sickle cell disease presents repeatedly with fever, musculoskeletal pain, and effusion into the knee joint. No infection or other arthritic disorder has yet been identified after repeated studies, and as the crisis subsides, so does the effusion of the knee. However, in all crises, it is imperative to exclude an underlying infection.

It is not infrequent for a patient to present with severe abdominal pain as the only manifestation of a crisis, and it is usually not difficult to distinguish this from an acute surgical abdomen. In general, the ischemic abdominal crisis is not accompanied by involuntary guarding, rebound tenderness, or pain that is well localized, and bowel sounds are usually present. Therefore, if signs of peritoneal irritation are evident, it is important to consider and exclude the possibility of an acute surgical abdomen.

Approximately 30 per cent of adults with sickle cell anemia have gallstones and these may be a cause of acute cholecystitis or biliary colic. However, such complications of sickle cell disease are not common, and only one of our patients has required surgery because of a stone in the common duct. In a small percentage of adults with SS disease who have an enlarged spleen, acute left upper quadrant pain may be precipitated by splenic infarction.

Most crises which we see are accompanied by musculoskeletal pains. Such pain is caused by ischemia and/or infarction of skeletal tissue. When a vital organ such as the brain,²³ lung, or heart appears to be functionally decompensating, a major catastrophe may be imminent; patients so affected must be treated vigorously (*vide infra*).

Since the painful crisis is largely due to occlusion of small arterioles and venules by the abnormally shaped cell, the objective of therapy is to unsickle or reduce the number of sickle cells by: 1) treating those conditions which may have potentiated the sickling phenomenon, 2) using therapeutic modalities which directly inhibit sickling, and 3) diluting SS erythrocytes by limited exchange with normal erythrocytes.

The first proposition in therapy of crisis is to treat dehydration and acidosis disturbances which are common in sickle cell crisis and which in themselves induce further sickling. For this, balanced electrolyte solutions, intravenous bicarbonate or oral sodium citrate,^{1,3} have been recommended. If there is any indication of an infection, appropriate cultures should be obtained (e.g., blood, sputum, urine, etc.) and the patient vigorously treated with antibiotics. It should be appreciated that sickle cell disease patients are more prone to develop pneumococcal and salmonella infections.

The second proposition in therapy, to reverse the sickled cell, is more difficult to accomplish. A varying number of sickled cells are irreversibly altered, and these cells are more prone to sludge in the microcirculation.⁴ Numerous modalities have been recommended to reverse sickling such as phenothiazines,²¹ corticosteroids,¹⁴ and low molecular weight dextran,²⁰ but none has been consistently effective.

Recent studies in our laboratory have demonstrated that hypotonic sodium chloride solutions can reverse sickling of deoxygenated sickled cells.¹⁰ As a consequence of these observations, we have been treating patients in crisis with rapid infusion of hypotonic saline and have had extremely favorable results. Not only is pain rapidly relieved, usually in less than 36 hours, but there is a concomitant decrease in circulating sickle cells as objective evidence of the beneficial effect.

After base-line blood samples are obtained for routine hematologic studies, serum electrolytes, and osmolality, and after it is ascertained that there is no cardiac or renal decompensation, the patient is given 5.0 ml. per kg. of body weight per hour of 0.45 per cent saline solution intravenously. If the urinary output is good, the rate of the infusion can be increased over the next several hours to a maximum of 10 ml. per kg. per hour. Usually a therapeutic response is evident before this rate is required. A decreasing serum sodium concentration or serum osmolality indicates that the infusion is being administered at a sufficiently rapid

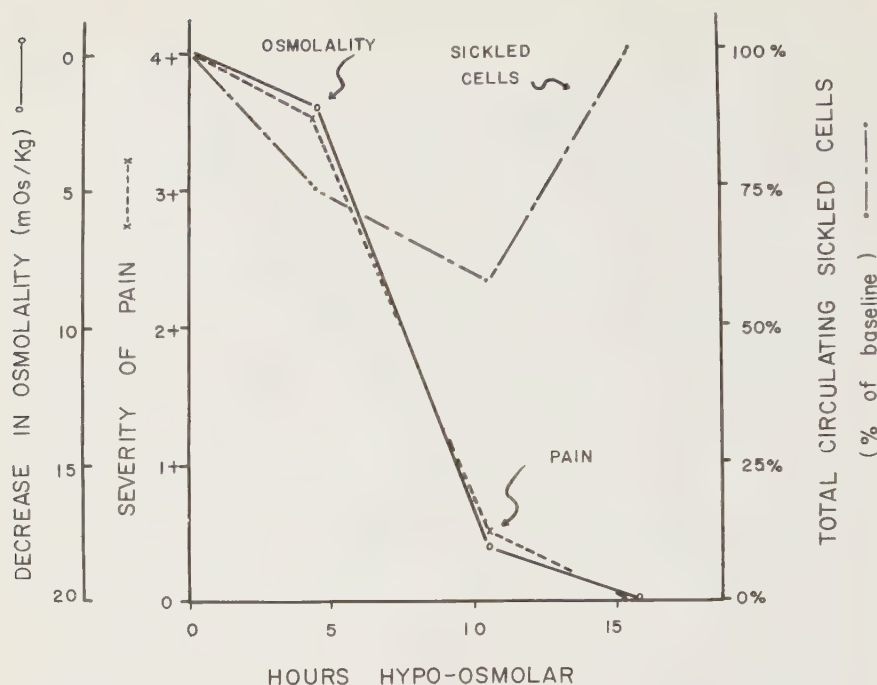


Figure 1. The effect of rapid infusion of hypotonic saline (0.45 per cent) on serum osmolality, number of circulating sickle cells, and pain in a patient with painful sickle cell crisis.

rate. One patient treated by us developed a mild increase in hemoglobinemia, but this did not result in any clinical problem. Such a phenomenon has also been noted in painful crises treated only symptomatically.¹⁹ We have noted no other untoward effects of this therapy.

The response of a typical patient is shown in Figure 1. It can be seen that after an initial decrease in circulating sickled cells, which paralleled the decrease in osmolality, the number then increased even though the patient remained free of pain. This finding was observed in several patients and suggests that there was improved circulation through tissues previously ischemic, resulting in release of sickled cells which were trapped during the crisis.

Recently, intravenous urea in invert sugar has been proposed for the treatment of crisis.¹⁸ Although urea solution in vitro appears to reversibly inhibit sickling, one problem with its clinical use is that urea causes an osmotic diuresis. Accordingly, voluminous amounts of fluids must be given to avoid catastrophic dehydration. We have no personal experience with this therapy, but would advise that it not be used unless one is carefully monitoring such patients in an intensive care unit.

The third proposition in therapy of crisis, to reduce the number of circulating SS cells, can be accomplished using limited exchange transfusions.⁵ We reserve this therapy for a crisis which appears intractable (lasting greater than 96 hours) or in which a vital organ appears compromised. We would recommend this therapy in a patient presenting with

evidence of a stroke, recurrent or massive pulmonary infarction, mesenteric infarction, or myocardial infarction (this last complication is rare). The procedure is not difficult and consists of replacing the patient's own blood with packed red cells unit for unit until the concentration of sickle cells is below 50 per cent of the concentration of erythrocytes. This can easily be monitored by counting the fraction of cells which sickle following exposure to metabisulfite. Usually, after 2 to 4 units have been exchanged, relief from pain is noted. Because of the obvious dangers of transfusion such as sensitization, febrile reactions, and the possibility of hepatitis, we try to limit the use of this therapeutic approach.

APLASTIC CRISIS

Under normal conditions erythropoiesis is an oscillating phenomenon subject to homeostatic negative and positive feed-back mechanisms. Hemolysis is a positive stimulator to erythropoiesis; evidence for this is seen in the concomitant reticulocytosis. Any situations which inhibit erythropoiesis by depressing erythroblast division or maturation in hemolytic disease will produce profound anemia, since peripheral red cell destruction continues. This is reflected in reticulocytopenia. Although infection may be a cause of such aplastic crises, frequently no etiology can be found. In sickle cell patients it is particularly important to avoid, if possible, drugs which are known to be toxic to hematopoiesis (e.g., chloromycetin).

The diagnosis of aplastic crisis in sickle cell disease requires a bone marrow analysis, since increasing anemia and reticulocytopenia may also be due to folate deficiency and megaloblastosis. With aplastic crisis there is a marked absence of erythroid precursors, perhaps a few proerythroblasts remaining, while in folate deficiency the erythroblasts have the characteristic megaloblastic appearance.

Not infrequently with the sudden exacerbation of anemia, a decreased intensity in scleral icterus may become apparent; this is a bedside clue to distinguish an aplastic crisis from a hemolytic crisis. The treatment of aplastic crisis should be prompt, for the anemia may progress quite rapidly. Packed red cells should be used daily in sufficient volume to maintain vital signs and function until erythropoiesis resumes. Daily reticulocyte counts should be obtained since a rise indicates recovery of erythropoiesis. For this reason, the hemoglobin concentration should not be raised much above that which is usual for the patient, since this would suppress erythropoiesis and reticulocyte output.

HEMOLYTIC CRISIS

Although the occurrence of sudden accelerated hemolysis is a rare cause of "crisis," we have seen a few patients in the past 10 years who presented with this complication in the absence of concomitant glucose-

6-phosphate dehydrogenase (G-6-PD) deficiency, sepsis, or other cause of hemolytic disease. In the presence of persistent reticulocytosis, and in the absence of bleeding, a rapid decrease in hematocrit suggests this complication. In all such cases, it is important to exclude infection or drug-induced hemolysis, such as might occur if there is concomitant G-6-PD deficiency. This genetic disorder is also commonly seen in the black population. The symptoms of the hemolytic crisis, like those of the aplastic crisis, are primarily due to increasing severity of anemia, but in this instance there is frequently an increase in the severity of jaundice. Treatment depends on the degree of the anemia and the symptoms. If transfusion proves necessary, packed red cells rather than whole blood should be used.

PREGNANCY AND SURGERY

Fertility is decreased in women with SS disease. When, however, pregnancy does occur and the patient is seen early in the first trimester, a frank discussion should be held to indicate the dangers both to herself and the fetus. There is sufficient evidence for increased morbidity to mother and fetus in SS disease to recommend abortion.^{6, 7, 11} If the decision is made to carry the pregnancy to term, while still controversial, we would suggest the use of limited exchange transfusion for patients in the third trimester with hematocrits in the low 20's until the per cent of sickle cells is reduced below 50 per cent.^{8, 17} One unit of packed cells can then be given every few weeks to maintain the hematocrit above 30 per cent. Fresh blood should be used from known donors. Although there are certainly risks to such a transfusion policy, the attendant danger of pregnancy to mother and fetus in sickle cell disease justifies such treatment. In addition to the usual prenatal vitamin and calcium supplements, these women should be given a few milligrams of folic acid daily. Iron, however, should be withheld since their stores have ample iron and, in addition, the transfused blood represents a considerable quantity of iron (approximately 225 mg. per unit).

The management of SS patients who require surgery depends on the nature of the surgery, the type of anesthesia, and the urgency of the situation. For elective major surgery, where general anesthesia is to be used (e.g., cholecystectomy and exploration of the common duct), preoperative daily partial exchange transfusions are given until the percentage of cells sickling with metabisulfite is less than 50 per cent. Hemoglobin electrophoresis is a simple technique to confirm this value. It is only necessary to remove two units of whole blood and infuse two units of packed cells every day for 5 to 6 days to achieve this. In emergency situations, one can exchange a substantial volume of blood in several hours by passing a catheter into the subclavian vein via the brachial vein. Fortunately, although we have used this system for total body exchanges for fulminating hepatitis, we have not had to use it in sickle cell anemia.

It should be emphasized that surgery in patients with SS disease is a team effort including the internist, surgeon, and anesthesiologist. Where

local or regional anesthesia is possible, it should be used, and when general anesthesia is required, adequate oxygenation is extremely important.

INFECTION

Patients with homozygous sickle cell disease have been known to be prone to certain infections, particularly pneumococcal pneumonia, sepsis, and meningitis,^{1,2} as well as salmonella sepsis and osteomyelitis.¹² The predisposition to such infections may be related to the absence of splenic function because of extensive infarction. Another contributing factor is the chronic hemolysis which may be saturating the phagocytic capacity of the reticuloendothelial system. It is important to recognize these infectious problems and to start antibiotics promptly after appropriate samples have been obtained for culture. Specific sensitivity studies, when reported from the laboratory, should be used to select the antibiotics. Until these are available we usually start with broad spectrum bactericidal drugs, such as a combination of cephalothin and kanamycin, rather than with bacteriostatic agents. If salmonella is suspected from the outset, the drug of choice is probably ampicillin, because of the danger of bone marrow suppression attendant to the use of chloromycetin.

INFARCTION

Bone infarcts are common in hemoglobinopathies involving sickle hemoglobin. They present as localized pain occasionally accompanied by heat, swelling, and tenderness over marrow-producing bone or long bones. They may be confused with an osteomyelitis, a condition which occurs far less commonly.

Splenic infarction, as described previously, may be a cause for acute left upper quadrant pain in patients with splenomegaly. The treatment for established splenic and bony infarcts is supportive with analgesics, but we still use hypotonic saline for localized sites of severe pain for such episodes may be secondary to ischemia without infarction.

Pulmonary infarction in sickle cell disease is a particularly difficult problem because the anoxia may precipitate additional crises. In addition to the usual clinical symptoms and signs of pulmonary infarction, examination of the peripheral blood smear may reveal blister cells and fragmented red cells as well as the usual sickle cells.²

Even though the pathogenesis of pulmonary infarction is pseudothrombosis as a consequence of the sludging of sickled erythrocytes, we nevertheless use heparin anticoagulation to prevent propagation of a thrombus which might result from reduced blood flow. Long term anticoagulation is not indicated, however, unless there is evidence of recurrent thrombophlebitis or other source of thromboembolism.

This discussion has concentrated primarily on patients with SS disease, but if the manifestation of SC or any combination of S and another abnormal hemoglobin is severe, the same therapeutic guidelines

may be used. This is particularly true for patients with SC disease. Although many have a mild course, some have severe painful crises. Pregnancy in SC women may be also attended by severe complications and these patients must have careful prenatal care.

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Acute Manifestations of Platelet Dysfunction

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A hemorrhagic diathesis may result from a vascular abnormality, a defect in thrombin generation owing to the inherited or acquired lack of plasma coagulation factors, hypofibrinogenemia, thrombocytopenia, or a qualitative platelet defect. This brief review will only be concerned with those bleeding disorders which result from the last, i.e., a defect in platelet function.

Like thrombocytopenia, a platelet function defect is usually manifested by easy bruising, spontaneous ecchymoses, prolonged bleeding after minor lacerations, and recurrent mucosal bleeding (epistaxis, menorrhagia, or rarely gastrointestinal hemorrhage). Except for the last, these complaints do not constitute medical emergencies. However, if such a history is unsought or ignored and the patient subjected to surgery—be it a tooth extraction, tonsillectomy, laparotomy, or thoracotomy—the possibility of life-threatening hemorrhage does arise. As with other bleeding disorders, the age at onset and the family history may be helpful in deciding whether one is dealing with an acquired or inherited disorder. In addition to a routine blood count, preliminary hematologic evaluation of the patient with a suspected bleeding diathesis should include a platelet count, a tourniquet test (in the absence of obvious purpura or severe thrombocytopenia), and a bleeding time test. A prothrombin time and partial thromboplastin time may help to rule out gross abnormalities in the plasma coagulation mechanism. An abnormality of platelet function should be suspected when a normal platelet count and a prolonged bleeding time are found concomitantly.

NORMAL HEMOSTASIS

A brief review of the role of platelets in normal hemostasis may provide a better understanding of these clinical findings and the tests used to assess platelet function.²⁸

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When a blood vessel is severed there is local vasoconstriction and exposure of the plasma and platelets to the collagen underlying the vascular endothelium. Platelets normally *adhere* to the collagen and to a recently described noncollagenous material underlying the vascular endothelium.¹ Platelet adhesion is followed by adenosine diphosphate (ADP) *release*. ADP is a potent platelet aggregating agent which leads to progressive local *platelet aggregation* to form a platelet plug which occludes the injured vessel.³⁰ Almost simultaneously, both the intrinsic and extrinsic systems of the blood coagulation cascade are activated, with the local generation of thrombin. The release of platelet phospholipid (platelet factor 3, or PF-3) accelerates thrombin formation. The thrombin leads to more platelet aggregation and the conversion of fibrinogen to fibrin to form a network of fibrin strands which stabilizes the platelet plug. Fibrin increases as platelets autolyze so that by 24 to 48 hours the hemostatic plug consists almost entirely of fibrin, which is gradually digested by normal fibrinolytic mechanisms as the defect is re-endothelialized.

Abnormalities of platelet adhesiveness, ADP release, aggregation, and phospholipid availability have been described in association with bleeding disorders.

TESTS OF PLATELET FUNCTION

Bleeding time. In the Ivy method,²⁰ capillary pressure is increased by applying 40 mm. Hg pressure with a sphygmomanometer and making duplicate incisions of standard depth and length on the volar surface of the forearm, using either a finger lancet or, for greater precision, a template.²⁶ The time required for bleeding to stop is then measured by blotting with filter paper or gauze every 30 seconds without disturbing the wound. The normal result is 3 to 6 minutes and the results are reproducible.¹¹

Clot retraction should be observed in recalcified plasma rather than whole blood. A semiquantitative estimate of clot retraction can be obtained by measuring the volume of plasma extruded from a given volume of recalcified plasma with a known concentration of platelets after incubation at 37° C. for a given time interval.¹¹

Platelet adhesion. In vivo platelet adhesion can be monitored by performing serial platelet counts on blood obtained from an actively bleeding, standardized laceration.² The adhesion of platelets to glass or collagen is taken as an in vitro parameter of this normal platelet function.¹² To assess platelet adhesiveness to glass, a specimen of native blood is passed immediately through a column of glass beads under standardized conditions of pressure, flow-rate, and temperature, and the platelet count of serial samples of effluent blood is compared with the circulating platelet count.¹¹ Normal values, which must be established for each laboratory under carefully standardized conditions, are usually expressed as the per cent retention of platelets in the glass bead column.

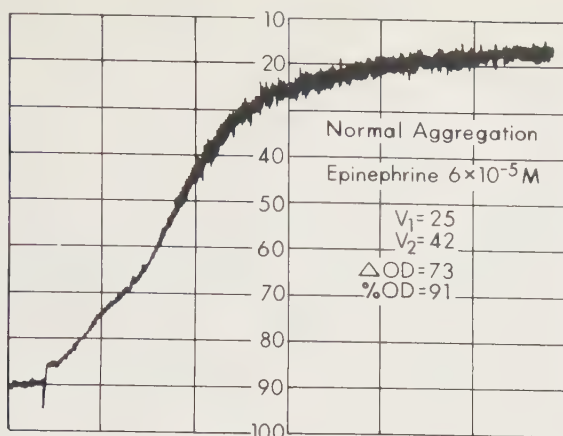


Figure 1. Biphasic wave of platelet aggregation after exposure of platelet-rich plasma to epinephrine. Indicated are the absolute and relative changes in optical density (OD); V_1 , the slope of the primary wave of aggregation; and V_2 , the slope of the secondary wave which is due to release of endogenous platelet ADP.

Platelet aggregation is evaluated in an "aggregometer"* which measures the optical density of a suspension of platelet-rich plasma before and after the addition of an aggregating agent such as epinephrine, collagen, or ADP.³ If the increased light transmission is plotted on a recording graph under the proper conditions a biphasic wave is inscribed (Fig. 1). The initial change is due to the added epinephrine, the second wave of aggregation to the release of endogenous ADP by the platelets.²³ This "release reaction" is an active process requiring the expenditure of metabolic energy.²¹ Epinephrine and collagen cause platelet aggregation via the release of endogenous platelet ADP. The secondary wave of aggregation is associated with the release of other platelet constituents, namely ATP, serotonin, and platelet factors 3 and 4 (a platelet protein with heparin antagonist properties).¹³ Fibrinogen is required for the reaction.¹² There is decreased aggregation with congenital hypofibrinogenemia¹⁹ and disseminated intravascular coagulation.²⁹

Platelet factor 3 availability. Prior to the more complete understanding of platelet aggregation and its relationship to the release reaction, many disorders of platelet function were described in association with a decreased availability of platelet factor 3. This abnormality may be a reflection of impaired aggregation and release, and as such may be only an indirect reflection of a decreased ADP content or impaired release. It can be estimated by comparing the kaolin recalcification time of platelet-poor plasma to that of plasma with a standard concentration of platelets per cubic millimeter.^{8, 11}

All or any one of these tests can be useful in defining abnormal platelet function as the basis for a bleeding disorder.

*Aggregometer, ChromO-Log, Inc., Broomall, Pennsylvania

BLEEDING DISORDERS DUE TO IMPAIRED PLATELET FUNCTION

INHERITED DEFECTS

Glanzmann's Thrombasthenia

Thrombasthenia (of Glanzmann⁶¹) is a rare, severe, familial bleeding diathesis which is transmitted as an autosomal recessive trait.⁴ Characteristically the bleeding time is prolonged and there is poor clot retraction in the presence of a normal platelet count. Platelet morphology is usually normal but morphologic abnormalities (including giant platelets, increased vacuolization, and bulls' eye appearance) have been described.³⁶ Platelet survival, megakaryocyte number, and morphology are normal.

The characteristic *in vitro* abnormality of platelet function is the absence of aggregation when tested with ADP. After exposure to ADP, thrombasthenic platelets undergo changes in shape without aggregation. Thrombin and collagen cause the shape change and endogenous ADP release, but again there is no platelet aggregation. Decreased PF_3 availability has been described and may be secondary to the lack of responsiveness to ADP, since PF_3 availability is normal when tested with prothrombin consumption or thromboplastin generation.⁴

When tested *in vivo*, or *in vitro* with glass beads, platelet adhesion is abnormal; but *in vitro* adhesion of platelets to collagen is normal. Platelet fibrinogen and thrombasthenin (a platelet contractile protein) are both normal. It is postulated that there is an undefined defect of the platelet membrane leading to its dysfunction.

Platelet transfusion during severe bleeding episodes or in preparation for surgery is the only effective therapy. Anovulatory therapy will control severe and persistent menorrhagia.

Von Willebrand's Disease

Von Willebrand's disease is a familial bleeding diathesis inherited as an autosomal dominant trait and is characterized by easy bruising, mucosal bleeding, and severe hemorrhage with surgical stress. When tested these patients have a prolonged bleeding time, a normal platelet count (rarely with abnormalities of platelet morphology³⁶), and a reduction in the plasma concentration of antihemophilic globulin (Factor VIII). In contrast with classical hemophilia, however, there is a delayed and sustained rise of Factor VIII concentration after transfusion with normal or hemophilic plasma.³⁰ Platelet aggregation and adhesion to collagen are normal, but there is abnormal adhesion of platelets to glass. The platelets themselves are not defective; rather, a plasma factor needed for normal platelet adhesion is lacking.²⁵ Infusion of plasma improves the adhesion of platelets to glass, replenishes the deficient factor VIII, and returns the bleeding time to normal for a brief time.

Although not conclusive, the evidence therefore suggests that patients with von Willebrand's disease lack a plasma factor responsible for

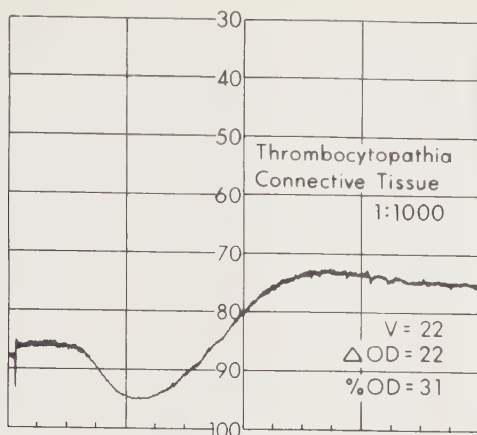


Figure 2. Impaired aggregation of platelets from a patient with thrombocytopathia. There is a delayed and diminished response to connective tissue.

normal platelet adhesion. This factor may be the biologically inactive factor VIII present in hemophilic plasma,¹⁹ since the latter corrects the bleeding time and causes a rise in the factor VIII level in these patients.⁴⁴ Infusions of cryoprecipitate are indicated for bleeding episodes and to prepare these patients for surgery.

Inherited Thrombocytopathia

This heading includes a group of bleeding disorders with normal platelet counts and prolonged bleeding times in which a variety of platelet function abnormalities have been demonstrated.^{9, 11, 31, 32, 39, 42} It is only since tests of platelet function have become better standardized and the effect of drugs on platelet function better understood that some classification of these diseases has become possible.¹⁷

There is at least one well defined pathogenetic mechanism involved in some of these patients and that is a failure of ADP release.^{16, 17} Because of the "platelet release abnormality," collagen-induced platelet aggregation is impaired (Fig. 2), the second wave of epinephrine-induced aggregation is diminished, and at 37° C. in vitro, disaggregation follows the initial wave of ADP-induced aggregation. The defect in some patients is due to an absence of the normal storage pool of adenine nucleotides in the platelet granules.¹⁶ This storage pool is distinct from the metabolic pool of adenine nucleotides. Sporadic¹⁷ and familial¹⁶ cases have been reported. In the latter, the inheritance pattern has been autosomal dominant with variable expressivity.

The platelets in this "storage pool disease" are often smaller than normal, but in some patients large platelets may be seen.¹⁷ The platelets also exhibit abnormal adhesion to glass beads and decreased platelet factor 3 availability. Albinism has been described in association with this defect.¹⁰ In some patients with impaired collagen-induced aggregation

the storage pool of ADP is normal and the defect seems to reside in the release reaction⁴⁷ (aspirin-like defect, see below).

There are a number of reports of familial and sporadic cases of bleeding caused by abnormal platelet function which cannot be easily categorized in terms of the specific defect involved. In most, the storage pool of adenine nucleotides has not been measured. They are clinically similar, with a history (often life-long) of "oozing and bruising."⁵⁰ The platelet counts are normal and the bleeding time prolonged. The most consistent abnormality has been a defect in epinephrine, collagen, or ADP-induced aggregation with variable results of platelet adhesion and PF-3 availability.

Bernard-Soulier syndrome is a rare disorder, inherited in an autosomal recessive manner and associated with the presence of very large platelets and variable thrombocytopenia due to decreased platelet survival. The bleeding time may be prolonged when the platelet count is normal, indicating a defect in platelet function which has not been accurately defined.

Wiskott-Aldrich syndrome is a rare, sex-linked recessive disease characterized by eczema, recurrent infections, and thrombocytopenia due to decreased platelet survival.⁷ The platelets are abnormally small, do not aggregate normally, and have a decreased storage pool of adenine nucleotides (and therefore resemble the platelets of patients with "storage pool disease," except for the thrombocytopenia and sex-linked inheritance). Hemorrhagic manifestations may be severe, but in the fully expressed syndrome severe infections are a greater threat: splenectomy is therefore contraindicated. In those variants of the syndrome in which thrombocytopenia is the major or only manifestation, splenectomy may be useful.

Other Thrombopathic Thrombocytopenias. A number of case reports describe sporadic and familial cases with co-existent thrombocytopenia and disordered platelet function.^{15, 22, 27, 31, 36, 38} The platelet function deficiencies were variable; in some instances there were characteristic morphologic abnormalities (agranular platelets, "the gray platelet syndrome"³⁶). Some patients benefited from splenectomy.

ACQUIRED DEFECTS

Uremia

A prolonged bleeding time, poor clot retraction, decreased platelet adhesiveness, and decreased platelet factor 3 availability have all been described in the bleeding diathesis seen in uremic patients.⁴⁰ These may all arise from the defect in ADP-induced platelet aggregation which is regularly seen in these individuals. The abnormal bleeding and platelet function are corrected by hemodialysis. In vitro exposure of platelets to a variety of compounds including creatinine, urea, and urates or to changes of pH or osmolality within the range seen in uremia does not induce similar abnormalities.⁴⁰ A metabolite of urea (guanidino succinic acid)¹⁸ and a phenolic acid³⁵ have each been implicated in producing the abnormality.

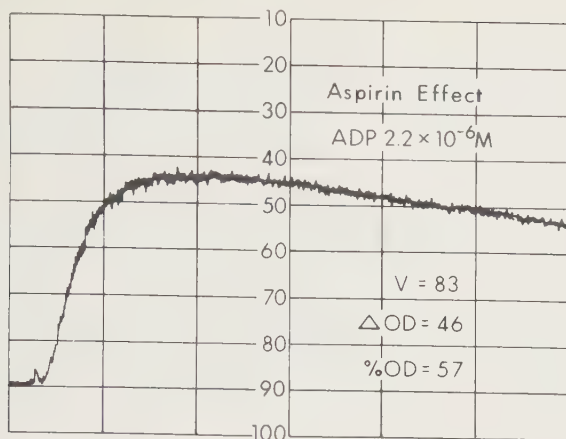


Figure 3. Aspirin-induced abnormality of platelet aggregation. After exposure to ADP, there is an initial wave of aggregation but no secondary wave due to inhibition of ADP release.

Drugs

Aspirin. A 1 gm. dose of aspirin will prolong the bleeding time of a normal individual by several minutes for 4 to 7 days without producing abnormal bleeding.²⁶ However, a bleeding diathesis may be precipitated in patients with an underlying plasma coagulation or platelet defect who are given small doses of aspirin. Therefore, this drug should be avoided in patients with renal failure, thrombocytopenia, or hereditary platelet or coagulation abnormalities.

Aspirin impairs collagen and epinephrine-induced platelet aggregation by an inhibition of endogenous ADP release¹³ (Fig. 3). This inhibition of the release reaction occurs with no decrease in the total amount of storage pool nucleotides.

Phenothiazines, antihistamines, and tricyclic antidepressants also inhibit the release of ADP by platelets, causing impaired aggregation.¹⁷

Prostaglandin E, methyl xanthine, and dipyridamole inhibit ADP-induced platelet aggregation directly. This effect has been attributed to their ability to increase cyclic AMP in the platelet.²⁹

High molecular weight dextran may prolong the bleeding time, decrease platelet adhesion, and interfere with platelet aggregation. It may act by coating platelets, thus preventing their interaction with various stimuli.⁴⁶

Dysproteinemia

In addition to hyperviscosity, delayed fibrin polymerization, and thrombocytopenia, abnormal platelet function may contribute to the bleeding diathesis seen in patients with myeloma and macroglobulinemia.³³ Again, platelet coating by the para-protein may cause the reported impairment of platelet adhesion and aggregation. Treatment should be directed at reducing the serum concentration of the abnormal protein, either by chemotherapy or plasmapheresis.

Liver Disease

The defect in ADP, thrombin-induced aggregation, and PF_3 availability may be due to circulating fibrinogen degradation products resulting from the enhanced fibrinolysis seen in some patients with severe liver disease.⁴¹

Disseminated Intravascular Coagulation

Fibrinogen is a necessary cofactor for ADP-induced platelet aggregation. Some of the larger fibrinogen degradation products inhibit ADP-induced platelet aggregation. In some cases the degradation products may complex with fibrinogen on the platelet surface and lead to aggregation.²⁹ Thus hypofibrinogenemia, platelet consumption, and impaired platelet function all contribute to the hemorrhagic phenomena seen in patients with disseminated intravascular coagulation.

Scurvy

Decreased platelet adhesiveness and absent spontaneous aggregation combine with the defect in the vascular wall to result in a bleeding syndrome.⁴⁸

Myeloproliferative Diseases

Abnormalities in all parameters of platelet function have been reported in acute and chronic myelocytic leukemia, polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, and some refractory anemias.^{3, 21} In some patients, the abnormal platelet function may be part of a preleukemic syndrome.⁴⁵

SUMMARY

The availability of relatively simple techniques for evaluating normal platelet function has led to the definition of a number of inherited and acquired disorders of platelet dysfunction. Better understanding and more widespread appreciation of these abnormalities will surely lead to improved patient care.

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Tests of Coagulation

Use and Interpretation

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Laboratory screening of coagulation is called for in evaluating two kinds of patients: those in whom a *hemorrhagic* diathesis is suspected, and those in whom a *thrombotic* diathesis (such as disseminated intravascular coagulation) is suspected. Routine preoperative evaluations should be by careful history and physical examination, and will require less detailed laboratory work. Young children who have not yet experienced the traumas of life will have a negative history and will require laboratory evaluation prior to surgery.

To identify and treat hemorrhagic or thrombotic disorders, one must understand the hemostatic mechanism and its laboratory evaluation.

THE HEMOSTATIC MECHANISM

Hemostasis begins at the site of blood vessel wall injury with platelets adhering to exposed subendothelial structures such as collagen. Collagen contact also causes a release reaction of platelet contents including adenosine diphosphate (ADP). ADP initiates platelet aggregation at the site of the lesion, resulting in further platelet release of ADP and growth of the platelet aggregate. Such platelet masses or aggregates, referred to as primary hemostatic plugs, can break up and be swept downstream if not stabilized. Stabilization is brought about by thrombin, which acts directly on platelets, causing degranulation, membrane disruption, and firmer platelet aggregation. Thrombin also converts fibrinogen to fibrin, resulting in fibrin deposition within the platelet ag-

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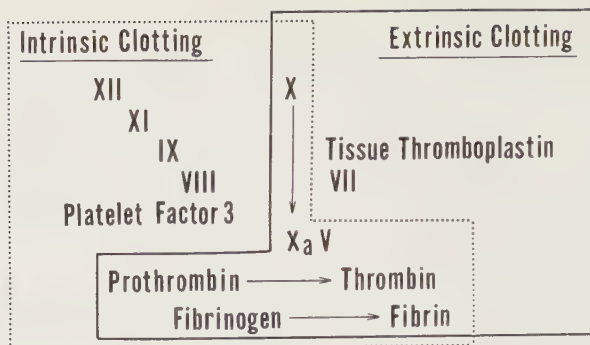


Figure 1. The intrinsic, extrinsic, and common pathways of blood clotting. The essential difference between intrinsic and extrinsic pathways is the method by which each produces an activator of factor X; by interaction of factors found in blood (in the intrinsic pathway), or by interaction of tissue thromboplastin, a factor not ordinarily found in blood, with factor VII (in the extrinsic pathway).

gregates. Thrombin does not normally circulate but is generated from its inert precursor in plasma, prothrombin, under conditions favoring coagulation. The generation of thrombin may proceed by either of two sets of chain reactions, the intrinsic and the extrinsic clotting reactions, both of which are essential for normal hemostasis (Fig. 1).

The intrinsic pathway of coagulation does not require anything added to blood. It is initiated by activation of Factor XII (Hageman factor)—*in vitro* by contact with glass surface, *in vivo* probably by contact with subendothelial collagen or perhaps other connective tissue components. As illustrated in Figure 1, this is the first of a series of chain reactions in intrinsic clotting. Unique to the intrinsic clotting mechanism are factor XII, factor XI (plasma thromboplastin antecedent), factor IX (plasma thromboplastin component, Christmas factor), factor VIII (antihemophilic factor) and platelet factor 3 (a platelet lipoprotein), which interact to form an activator of factor X.

The extrinsic clotting mechanism requires the addition of a factor not ordinarily present in blood. This factor is tissue thromboplastin, a lipoprotein found in tissue cells, particularly in the brain, lung, and placenta, and also to a lesser extent in the vessel wall. Under certain pathologic circumstances (such as gram-negative sepsis) leukocytes can produce tissue thromboplastin and contribute to disseminated intravascular coagulation. Tissue thromboplastin reacts in the presence of calcium with a plasma protein, factor VII (proconvertin), which is unique to the extrinsic system, to form an activator of factor X.

Thus the difference in these two pathways is the method by which each produces an activator of factor X.

Subsequent reactions are common to both systems. Factor X is converted to its active form X_a , which, in the presence of factor V and a phospholipid present in either platelets or tissue thromboplastin, forms prothrombin activator, which rapidly converts prothrombin to thrombin. Thrombin thus generated enzymatically splits two polypeptides from fibrinogen, producing fibrin monomer. Fibrin monomers then polymerize to form a mesh of fibrin strands which is readily soluble in 5M urea or 1

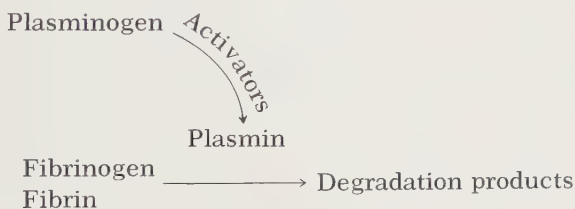
per cent monochloroacetic acid. In the presence of ionized calcium, thrombin also converts factor XIII (fibrin stabilizing factor) to its active form. The active form of factor XIII produces cross linking between fibrin molecules, resulting in fibrin clots which are more stable and no longer soluble in urea or monochloroacetic acid.

Clot retraction which may or may not be of importance in hemostasis occurs following the formation of fibrin by thrombin in the presence of platelets and ionized calcium or magnesium.

Hereditary or acquired deficiencies or inhibitors of any of the coagulation factors, except factor XII, are associated with bleeding disorders; therefore, all must be evaluated in a complete screening of coagulation.

FIBRINOLYSIS

Activation of the hemostatic mechanism and deposition of fibrin both activate the fibrinolytic enzyme, plasmin. Plasmin is a proteolytic enzyme which attacks fibrinogen or fibrin, producing degradation products which are eventually cleared from the circulation by the reticuloendothelial system. Plasmin does not circulate normally, but is present as an inert precursor, plasminogen, which must be activated.



LABORATORY TESTS OF HEMOSTASIS: COAGULATION AND FIBRINOLYSIS

The best screening test for the existence of a disorder of the hemostatic mechanism is provided by a careful history and physical examination. When such examination or the clinical setting suggest that an abnormality exists, the laboratory tests undertaken should evaluate primary hemostatic plug formation, the intrinsic and extrinsic clotting pathways, fibrinogen to fibrin conversion, and fibrinolysis.

Tests of Hemostatic Plug Formation and Platelet Abnormalities

The bleeding time is a reflection of primary hemostatic plug formation and therefore is not ordinarily affected by abnormalities in coagulation. It is best determined by the Ivy method which utilizes a blood pressure cuff around the upper arm inflated to 40 mm. Hg. The original test utilized three puncture wounds of the forearm; however, the test is more sensitive and reproducible if small incisions of the skin (10 mm. long and 1 mm. deep) are made with a number 11 scalpel blade. This test

Table 1. *Defects of Platelet Function*

	VON WILLEBRAND'S DISEASE	GLANZMANN'S THROMBASTHENIA	THROMBOPATHIA (Platelet Release Abnormality)
Bleeding Time	Prolonged	Prolonged	Prolonged
Platelet retention in glass bead columns	Diminished	Diminished	Diminished
Aggregation with:			
1. ADP	Normal	Abnormal	Abnormal ^a
2. Collagen	Normal	Abnormal	Abnormal
3. Epinephrine	Normal	Abnormal	Abnormal
Kaolin-induced platelet factor 3 activity	Normal	Abnormal	Variable
Clot retraction	Normal	Absent	Normal

^aOnly the secondary wave of aggregation is abnormal.

adds little or no useful information in the presence of significant thrombocytopenia; therefore, a platelet count or an estimate of the platelet count by examination of a well-made and stained blood smear should precede this test. The test is also of little value in patients with known impaired hemostatic plug formation, such as in severe uremia or following ingestion of aspirin. It is useful in evaluation of patients suspected of having von Willebrand's disease or a qualitative platelet abnormality. If a qualitative defect of platelets is suspected other tests (such as clot retraction, platelet retention in glass bead columns, aggregation by collagen, ADP, or epinephrine, and kaolin-induced platelet factor 3 activity) can be utilized to confirm and classify the abnormality (see Table 1).

Tests of the Blood Clotting Pathways

Intrinsic blood clotting can be evaluated by a clotting time. However, this crude test may fail to detect all but the most severe clotting factor deficiencies. Observation of whole blood clotting is useful in evaluation of clot retraction and fibrinolysis. The partial thromboplastin time (PTT), a much more sensitive test for the evaluation of the intrinsic pathway, is almost always abnormal when any of the plasma clotting factor activities involved are reduced to levels which result in abnormal hemostasis. It is prolonged by low levels of factors XII, XI, IX, VIII, X, V, II (prothrombin), or I (fibrinogen), by inhibitors of these factors, or by inhibitors of one of the reactions involved.

The Quick prothrombin time is a sensitive test for the plasma clotting factors involved in the extrinsic pathway. It is prolonged by significant decrease in the plasma levels of Factors VII, X, V, II, or I, by inhibitors of these factors, or by inhibitors of one of the reactions involved. In some laboratories, absorbed plasma reagents containing Factor V and fibrinogen are added to the clotting mixture. Though this modified test is still referred to as a prothrombin time, it will no longer be affected by the levels of factor V or fibrinogen in the test plasma.

The thrombin time test, a measure of the conversion of fibrinogen to fibrin by a dilute thrombin, is prolonged by low levels of fibrinogen or inhibitors of the reaction. When done with human thrombin from Ortho Pharmaceutical, it is called the Fibrindex test.

By utilizing these three screening tests of coagulation, the PTT, the prothrombin time and the thrombin time, it is possible to categorize and partially identify coagulation abnormalities.

1. Prolonged PTT, normal prothrombin time, and normal thrombin time: This combination of findings limits the defect to a deficiency, or an inhibitor, of those clotting Factors (XII, XI, IX and VIII) unique to the intrinsic coagulation mechanism. Correction of the PTT by addition of normal plasma to the test system indicates a deficiency; failure to correct indicates an inhibitor. Inhibitors of factors VIII and IX have been well documented. Significant prolongation of the PTT in the absence of a hemorrhagic diathesis is suggestive of factor XII deficiency, or rarely a clinically inapparent factor XI deficiency. Identification of a deficiency of these factors can be ascertained by determining the corrective effect of the test plasma on the prolonged PTT of plasmas with known deficiencies. Plasmas with known specific factor deficiencies are available commercially.

2. Normal PTT, prolonged prothrombin time, and normal thrombin time: These findings are characteristic of factor VII deficiency. The prothrombin time is corrected by normal plasma or aged serum, but not by absorbed plasma or serum or plasma from an individual with known VII deficiency. An inhibitor of factor VII has not been reported. The same pattern, but with only a slightly prolonged prothrombin time, is sometimes seen as a mild manifestation of the situation described in the following paragraph.

3. Prolonged PTT, prolonged prothrombin time, and normal thrombin time: Such a coagulation profile is indicative of an abnormality in both the intrinsic and the extrinsic pathways prior to the reaction of thrombin on fibrinogen. Single deficiencies of factors V, X, or prothrombin can account for such findings, since these factors are involved in both pathways. However, such findings are also encountered with multiple deficiencies affecting both pathways—for example, hepatocellular disease (factors II, V, VII, IX, X), vitamin K deficiency, or warfarin administration (II, VII, IX, X). If screening tests are corrected by the addition of normal plasma, the abnormality is due to a deficiency of one or more of the clotting factors as indicated above, and specific assays can identify the factors. If normal plasma does not correct the screening tests, the abnormality is due to an inhibitor. Two inhibitors have been reported which could give these findings, one against factor V, and the other the inhibitor seen in lupus erythematosus which appears to inhibit the reaction between prothrombin activator and prothrombin.

4. Prolonged PTT, prolonged prothrombin time, and prolonged thrombin time: These findings can be caused by hypofibrinogenemia or afibrinogenemia, by dysfibrinogenemia, or by an inhibitor of thrombin or fibrin monomer polymerization, with or without deficiencies of factors required in earlier steps. Since the thrombin time is a more sensitive test

of the final step of coagulation, the conversion of fibrinogen to fibrin and polymerization with gel formation, it can be prolonged when both the PTT and prothrombin time are normal. Such findings would eliminate an abnormality of the coagulation up to this point. Correction of the thrombin time by the addition of normal plasma or fibrinogen to the test system is characteristic of a deficiency of fibrinogen. Failure to correct is indicative of an inhibitor and of some forms of dysfibrinogenemia. The same principle can be used to see if a prolonged PTT or prothrombin time is due to the presence of an inhibitor. The inhibitors of the thrombin time most commonly encountered are heparin, products of plasmin digestion, and some myeloma proteins.

Because the thrombin time is prolonged by the presence of fibrin degradation products, it also serves as a screening test for secondary fibrinolysis (e.g., lysis of fibrin formed during disseminated intravascular clotting). The much rarer case of primary fibrinolysis will also be detected. There are several other tests for fibrinogen and fibrin degradation products in use but not usually readily available, some of them capable of giving quantitative data, but the thrombin time plus examination of the blood clot will ordinarily suffice. These tests are the staphylococcal clumping test, the tanned red cell hemagglutination inhibition immunoassay, a modification of the Fi-test, and other immunologic techniques.

The plasma protamine paracoagulation test is used to detect fibrin monomer in citrated plasma. Soluble complexes of fibrin monomer with fibrinogen and fibrin split products will precipitate as fibrin strands when protamine is added. This is a very sensitive test for detecting prior coagulation, such as disseminated intravascular clotting, and sometimes, even thrombophlebitis. Extreme care must be taken to avoid false positives resulting from slight *in vitro* clotting which can occur when there is difficulty performing a venipuncture or when blood is collected from a catheter left in a vein. Disseminated intravascular coagulation will usually result in multiple factor abnormalities (e.g., factor V, factor VII, prothrombin) and prolonged PTT and prothrombin time.

Factor XIII deficiency may be missed by all of above tests. To detect it, a clot of the patient's plasma is allowed to stand overnight at 37° C. in 5M urea. A normal clot will not dissolve, but a factor XIII deficient clot will.

INTERPRETATION OF TESTS OF COAGULATION IN A CLINICAL SETTING

Case 1

An 8 year old boy with a lifelong history of recurrent hemarthroses was brought to the emergency room in a wheel chair with a swollen painful right knee. Whole blood clotting time was 52 minutes and PTT 240 sec./control 35 sec. Bleeding time, prothrombin time, and thrombin time were normal. This patient, a classic hemophiliac, was found to have a factor VIII level of 1 per cent of normal by assay.

Case 2

A 33 year old man, a chronic alcoholic and drug addict, presented to the emergency room with bleeding from a knife wound of the skin over the knee. The bleeding had not stopped after direct pressure. There was no prior history of a bleeding abnormality, and physical examination was normal except for tachycardia. Surgical closure did not completely stop the bleeding. A pressure dressing was applied and a transfusion begun to replace the now extensive blood loss. During the 4 unit transfusion the bleeding stopped and did not recur. At a later date he was evaluated and the following tests were normal: bleeding time, Quick prothrombin time, thrombin time, whole blood clotting time and clot retraction. The PTT was 124 sec./control 35 sec. The factor VIII level was 15 per cent of normal by assay. This patient had a mild hemophilia.

Case 3

A 26 year old woman was brought to the emergency room unconscious and hypotensive after taking a "bottle of sleeping pills." In the emergency room an endotracheal tube was placed and the stomach lavaged via nasogastric tube. A house officer performed a cutdown and because he had some difficulty with the procedure he "flushed out the intravenous catheter with heparin." This was not known to the rest of the medical staff. The patient was then sent upstairs to a ward where she was noted to be bleeding from both nostrils, from the endotracheal tube, from the cutdown site, and from venipuncture sites. The whole blood clotting time, PTT, Quick prothrombin time, and thrombin time all failed to clot. A mixture of half normal plasma and half patient's plasma was prepared and it failed to clot in the thrombin time test. Protamine was added to the patient's plasma and it now clotted in the thrombin time test. A diagnosis of heparinemia was made and 50 mg. of protamine was given intravenously. The bleeding stopped at once; 24 hours later all coagulation tests were normal. She recovered uneventfully and it was during her recovery that it was learned that she had been given heparin.

Table 2. *Usual Laboratory Results in Some Clinical Disorders of Hemostasis*

	BLEEDING TIME (hemostatic plug formation)	PTT (intrinsic clotting)	QUICK PROTHROMBIN TIME (extrinsic clotting)	THROMBIN TIME (fibrinogen to fibrin conversion)	PROTAMINE TEST (presence of soluble fibrin)
Hemophilia	Normal	Prolonged	Normal	Normal	Negative
Vitamin K deficiency or antagonism (coumarin)	Normal	Normal to prolonged	Prolonged	Normal	Negative
Heparinemia	Normal	Prolonged	Prolonged (often only slightly)	Prolonged	Negative
Thrombocytopenia	Prolonged	Normal	Normal	Normal	Normal
Disseminated intravascular coagulation	Prolonged	Prolonged	Prolonged	Prolonged	Positive
Extensive thrombosis	Normal	Normal	Normal	Normal	Positive

Case 4

A 42 year old woman underwent radical vulvectomy for squamous cell carcinoma of the vulva several years prior to this admission and suffered no unusual bleeding. Because of recurrent disease and intractable pain, a percutaneous cervical spinal cord tractotomy was performed. A hematologist was called when bleeding from the needle puncture in the neck was unresponsive to direct pressure and was continuous for 24 hours. The partial thromboplastin time was 80 sec./control 35 sec., prothrombin time 40.2 sec./control 12 sec. The bleeding time, whole blood clotting time, clot retraction and thrombin time were all normal. It was also noted that she had been on prolonged oral antibiotics for a urinary tract infection. A provisional diagnosis of vitamin K deficiency from oral antibiotics was made and the patient was given 10 mg. of vitamin K₁ parenterally. The bleeding stopped in 6 hours and the laboratory tests subsequently returned to normal.

The expected laboratory results in some disorders, including those recounted in this section, are summarized in Table 2.

SUMMARY

Most clinical disorders of coagulation can be detected by a careful history and physical examination and use of the widely available screening tests we have described. In most cases a presumptive specific diagnosis can be reached. In some cases more refined tests are needed to identify the specific defect.

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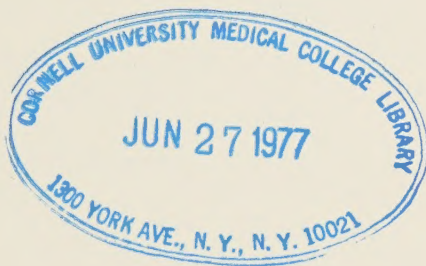
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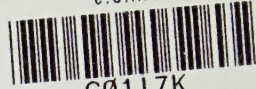
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